



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-042

NDA 21-052

5/7/01

Merck & Co., Inc.
 Attention: Robert E. Silverman, M.D., Ph.D.
 Senior Director, Regulatory Affairs
 Sumneytown Pike
 P.O. Box 4, BLA-20
 West Point, Pennsylvania 19486

Dear Dr. Silverman:

Reference is made to your Proposed Pediatric Study Request submitted on August 23, 2000, for Vioxx (rofecoxib).

To obtain needed pediatric information on rofecoxib for the treatment of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies. Please note that since the efficacy and safety of rofecoxib in adult rheumatoid arthritis (RA) has not been established by adequate and well controlled trials, in addition to the pharmacokinetic data, an indication for JRA would require replicated evidence of efficacy in the pediatric population. This Pediatric Written Request may be amended upon completion of the review of the adult RA efficacy supplement.

Types of studies:

Study 1: Pharmacokinetic study in patients with Juvenile Rheumatoid Arthritis (JRA).
 This requirement may alternately be fulfilled by more than one study.

Studies 2 & 3: Clinical safety and efficacy studies

Objective/rationale:

Study 1: To evaluate the pharmacokinetics of rofecoxib in children with JRA.

Studies 2 & 3: The objectives of these studies should be to evaluate the safety and the clinical efficacy of rofecoxib in patients with JRA.

Indication to be studied:

Studies 2 & 3: Rofecoxib will be studied for the treatment of the signs and symptoms of JRA.

Study Design:

- Study 1: The study should be a multiple dose pharmacokinetic study with a pharmacokinetic sampling plan covering the first dose as well as pharmacokinetic sampling at steady state.
- Study 2: This study should be a three-month or more, randomized double-blind, three-arm (two dosages, one active control), efficacy/safety, fixed dose, dose-response trial, followed by at least a nine-month open label extension. The active control and its dose should be generally accepted as a therapeutic option in the pediatric rheumatology community and should be justified as such. Prior use of the chosen comparator should be addressed.
- Study 3: This study should be a three-month or more, randomized, double blind, controlled, efficacy study in patients with JRA.

Age group and population in which study will be performed:

- Study 1: Patients with JRA approximately between the ages of 2-16 years should be studied, with at least one third of the patients approximately evenly distributed below the age of 6 years.
- Studies 2 and 3: These studies should include patients with polyarticular and pauciarticular (at least joints) course JRA. The inclusion of approximately 10% or more of patients with systemic course JRA is encouraged.
- Patients should be allowed to continue receiving standard-of-care therapy as indicated.
- The patient distribution should be approximately 2-16 years of age, with at least 30% of patients being <6 years of age.

Number of patients to be studied or power of study to be achieved:

- Study 1: In order to provide a sufficiently accurate estimate of any dosing adjustments that may be needed in pediatric patients, the planned pharmacokinetic evaluation should be powered and structured to detect a 30% change in drug clearance and other relevant pharmacokinetic parameters compared to such values for adult rheumatoid arthritis patients. The total volume of blood to be drawn and the PK methods to be employed in the data analysis should be determined a priori and stated in the protocol. If sparse sampling methods, i.e., population PK are employed, blood samples should be dispersed throughout the absorption and elimination phases of the drug concentration time profile to ensure proper parameter estimation.
- Studies 2 & 3: The studies should be powered to show that rofecoxib is not inferior to the active comparator (non-inferiority design) using the following criteria for non-inferiority: two-sided 95% confidence interval (CI). of treatment difference in improvement rates should be within 25% of the control's response rate.

Clinical Endpoints:

Study 1: The primary pharmacokinetic analysis should attempt to include all the patients in the study (with determination of both single dose and steady state AUC, C_{max}, T_{max} and CL/F).

Studies 2 & 3: The primary efficacy endpoint should be the JRA 30 Definition of Improvement (JRA-DOI), but assessment of additional efficacy variables outside the JRA core set is encouraged.

Drug Specific safety concerns:

Safety should be assessed by soliciting reports of adverse events, clinical laboratory evaluations and physical examinations. All safety data, especially data that may reflect potentially important events in a subset of patients (e.g. iritis for pauciarticular disease), should be collected and evaluated with descriptive statistics.

In addition to the safety concerns inherent to the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the adult rheumatoid arthritis populations (e.g. gastrointestinal bleeding, renal toxicity, liver toxicity, allergic reactions, etc), generic pediatric concerns such as growth and development should be addressed.

Patients with systemic course JRA often develop disseminated intravascular coagulation (DIC) when their disease is active and they are on NSAIDs, therefore it is of great importance to collect some safety data on these patients. If patients with systemic course JRA are included in the study, coagulation parameters, fibrinogen, fibrinogen split products and D-dimers should be collected.

Study evaluation:

Study 1: The effect of age on pharmacokinetic parameters will be evaluated. For the pharmacokinetic evaluation, the pharmacokinetic parameters calculated should be compared to either an adult rheumatoid arthritis control group or historical pharmacokinetic data in patients with adult rheumatoid arthritis.

Studies 2 & 3: Rofecoxib should be compared to a standard active control.

Drug Information:

- **Route of administration:** oral
- **Formulation:** appropriate formulation for a pediatric population.

Statistical information (statistical analyses of the data to be performed):

Study 1: Analysis of the pharmacokinetic parameters (e.g., C_{max} and AUC) should include a descriptive summary statistics for each parameter.

Studies 2 & 3: Three efficacy hypotheses should be formally tested – two equivalence (non-inferiority) tests, ruling out a clinically meaningful difference between each of the two rofecoxib doses and the active control and one difference test comparing the two rofecoxib dosages used. Another option is to demonstrate superiority of rofecoxib to the active comparator. Multiplicity issues should be considered. Safety data should be analyzed by descriptive statistics.

Labeling that may result from the studies:

Information collected from this study should permit the determination of appropriate labeling for the use of rofecoxib in JRA.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency should be submitted addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the studies:

Studies 1, 2, & 3: Reports of the above studies should be submitted to the Agency on or before December 31, 2003. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission “**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**” in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission “**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a **new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission “**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**” in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183), mail or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked “**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

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We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Sandra Folkendt, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Jonca C. Bull, M.D.
Deputy Director, ODE V
Acting Director, Division of Anti-Inflammatory,
Analgescic, and Ophthalmic Drug Products
Center for Drug Evaluation and Research

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/s/

Jonca Bull

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