DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-042
NDA 21-052

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 correspondence dated September 10, 2001, requesting changes to FDA's May 07, 2001, Written Request for pediatric studies for rofecoxib. Please note that the following Written Request supercedes that of May 07, 2001, which is no longer valid.

To aobtain needed pediatric information ion 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, pursant 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 inpatients with Juvenile Rheumatoid Arthritis (JRA). This requirement may alternately be fulfilled by more than one study.

Study 2: Clinical safety and efficacy study.

Objective/rationale:

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

Study 2: The objective of these studies should be to evaluate the safety and the clinical efficacy of rofecoxib in patients with JRA.

Indication to be studied:

Study 2: Rofecoxib will be studied for the treatment of the signs and symptoms of JRA.

Study Design:

Study 1: The study should be multiple dose pharmacokinetic study with pharmacokinetic sampling at steady state.

Study 2: This study should be a 12-week or more, randomized, double-blind, three-arm (tow dosages, one active control), efficacy/safety, fixed dose, dose-response trial, followed by at least 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.

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.

Study 2: These studies should include patients with polyarticular and pauciarticular (at least one joint) 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 10% of Patients being < 5 years of age.

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

Study 1: The sponsor's proposal to use age appropriate dosage forms, such as suspension for patients between the age 2-16 years and oral tablets for the patients older than 11 years is acceptable. In order to provide a sufficient accurate estimate of any dosing adjustments that may be needed in pediatric patients, the planned phamacokinetics evaluation should be powered and structured to detect a 30% change in mean apparent oral clearance (CL/F) and other relevant pharmacokinetic parameters compared to such values for adult rheumatoid arthritis patients. The 30% difference is based on mean change and is not based on confidence interval.

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.

Study 2: The study should be powered to rule out a clinically meaningful difference (adequately justified and prospectively defined) between at least one rofecoxib dose and the active control (equivalence hypothesis) or to demonstrate that rofecoxib is superior to the active control.

Clinical Endpoints:

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

Study 2: 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. Since COX-2 is constitutively expressed in the brain, potential effects in a developing central nervous system should be considered.

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 historical adult control group.

Study 2: 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: 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: 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 hyour reports of studies in response to this Written Request.

Reports of the studies that meet the terms of the Written Request dated May 07, 2001, as amended by this letter must be submitted to the Agency on or before December 31, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. Please 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 SUPPLEMENT TO YOUR 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) 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.

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 to the pediatric population.

If you have any questions, contact Barbara Gould, Regulatory Project Manager, at 301 827-2090.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Deputy Director, and Acting Director,
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonca Bull

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