



IND 48,395

G.D. Searle & Co.
Attention: Eva Essig, PhD, Associate Director
Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, IL 60077

Dear Dr. Essig:

Reference is made to your Proposed Pediatric Study Request submitted on August 11, 2000 and March 9, 2001 for celecoxib to IND 48,395 and further discussions with the Division on November 17, 2000 and on July 26, 2001.

To obtain needed pediatric information on celecoxib for the treatment of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA), the Food and Drug Administration (FDA) is hereby issuing to you an official amended Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act.

FDA requests that you submit information from the following study:

Type of study:

Clinical pharmacokinetic, safety and efficacy study in patients with JRA

Objective/rationale:

- To evaluate the pharmacokinetics of celecoxib in children with JRA
- To evaluate the efficacy of two doses of celecoxib compared to a standard active control (equivalence or superiority hypotheses), to evaluate the efficacy of celecoxib by dose-response (a difference hypothesis), and to evaluate the safety relative to the active control (descriptive statistics).

Indication to be studied:

Celecoxib will be studied for the treatment of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA).

Study Design:

- For the safety and efficacy evaluation, the study should be a three-month, randomized, double-blind, three-arm (two dosages, one active control), parallel, efficacy/safety, fixed-dose, dose-response trial, followed by a three-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.

- For the pharmacokinetic evaluation, multiple doses should be evaluated with a pharmacokinetic sampling plan at steady state. Pharmacokinetic sampling should occur at defined visits during the 12 week blinded period with sample times dispersed throughout the absorption and elimination phases.

Age group and population in which study will be performed:

- Patients with JRA between the ages of 2-16 years should be studied, with at least 10% of patients being < 5 years of age.
- Inclusion of patients with polyarticular and pauciarticular (at least 1 joint) course JRA. Since safety concerns exist for the use of non-steroidal anti-inflammatory drugs in patients with systemic onset JRA, inclusion of approximately 10% of patients of this type is encouraged.
- Patients should be allowed to continue receiving standard-of-care therapy as indicated.

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

- The study should be powered to detect a statistically significant difference between treatment groups. 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 compared to that observed for adult rheumatoid arthritis patients. The total volume of blood to be drawn and the pharmacokinetic 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 pharmacokinetics, are employed, blood samples should be dispersed throughout the absorption and elimination phases of the drug concentration time profile to ensure proper parameter estimation.
- The study should also be powered to rule out a clinically meaningful difference (prospectively defined) between at least one celecoxib dose and the active control (equivalence hypothesis) or to demonstrate that celecoxib is superior to the active control.

Clinical Endpoints:

- The primary pharmacokinetic analysis should include a sufficient number of patients in the study to detect a 30% difference in apparent clearance between JRA and adult RA patient populations.
- The primary efficacy endpoint should be the JRA 30% Definition of Improvement (JRA-DOI), but assessment of other 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 population (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 development 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 onset JRA have a systemic flare (become active) during the study, coagulation parameters (fibrinogen, fibrinogen split products and D-dimers) should be collected.

Study Evaluation:

- 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. The adult rheumatoid arthritis control group should be identified prior to initiating the study or justified based on review of all relevant pharmacokinetic studies in adult rheumatoid arthritis.
- For the safety and efficacy evaluation, celecoxib should be compared to the 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):

- The pharmacokinetic parameters calculated should be analyzed by descriptive statistics.
- Three efficacy hypotheses should be formally tested – two equivalence (non-inferiority) tests, ruling out a clinically meaningful difference between each of the two celecoxib doses and the active control; and one difference test comparing the two celecoxib dosages used. Another option is to demonstrate superiority of celecoxib to the active comparator. 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 celecoxib in JRA.

Format of reports to be submitted:

A full study report should be submitted to the Agency, addressing the issue outlined in this request with full analysis, assessment, and interpretation.

Time frame for submitting reports of the studies:

Study reports should be submitted to the Agency on or before December 31, 2005. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your study report in response to this Written Request.

Please submit a protocol 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 these studies should be submitted as an NDA or as a supplement to your approved celecoxib NDA with the proposed labeling you believe would be warranted based on the data derived from these studies. When submitting the report of this pediatric study, please clearly mark your submission, **“SUBMISSION OF PEDIATRIC STUDY REPORT – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font bolded types 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 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 Requests 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, please contact Ms. Jane Dean, RN, MSN, Project Manager, at (301) 827-2040.

Sincerely yours,

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