DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51, 268
NDA 20-938
NDA 21-530

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Jeffrey R. Snyder
Senior Associate Director
Drug Regulatory Affairs
900 Ridgebury Road,
P.O. Box 368
Ridgefield, CT 06877

Dear Mr. Snyder:

Reference is made to your Proposed Pediatric Study Request submitted on August 06, 2004 for Mobic® (meloxicam) Tablets 7.5 mg and 15 mg and Suspension 7.5 mg/5 mL to IND 51,268.

To obtain needed pediatric information on meloxicam for the treatment of the signs and symptoms of polyarticular and pauciarticular type Juvenile Rheumatoid Arthritis (JRA) as defined by the American College of Rheumatology criterion, in pediatric patients 2 years to < 17 years of age, 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. In addition to the pharmacokinetic data, an indication for polyarticular and pauciarticular type JRA would require evidence of efficacy and safety in the pediatric population.

Types of studies:

Study 1: Pharmacokinetic studies that will allow full characterization of meloxicam pharmacokinetics in patients with Juvenile Rheumatoid Arthritis (JRA).

Studies 2 & 3: Clinical safety and efficacy studies

Objective/rationale:

Study 1: To evaluate the pharmacokinetics of meloxicam in children and adolescents, 2 years to < 17 years of age, with JRA.

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

Indication to be studied:

Studies 2 & 3: Meloxicam will be studied for the treatment of the signs and symptoms of polyarticular and pauciarticular type JRA in pediatric patients 2 years to < 17 years of age.

Age group and population in which study will be performed:

Study 1: Patients with JRA approximately evenly distributed between the ages of 2 and < 17 years should be studied, with at least one third of the patients approximately evenly distributed below the age of 6 years.

Studies 2 & 3: Studies should preferably include a balance of patients with polyarticular and pauciarticular (at least 2 joints) course JRA. If patients with monoarticular disease (pauciarticular course) are included, separate statistical analyses will be required. The inclusion of approximately 5% to 10% or more of patients with systemic course JRA is recommended.

Patients should be approximately evenly distributed between the ages of 2 and < 17 years, with at least one third of the patients approximately evenly distributed below the age of 6 years.

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 JRA patients, the planned pharmacokinetic (PK) evaluation should be powered and structured to detect a 30% change in drug clearance. 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 study should be powered to rule out a clinically meaningful difference (adequately justified and prospectively defined) between meloxicam and the active comparator (equivalence hypothesis) or to demonstrate that meloxicam is superior to the active control.

Study Design:

Study 1: The conducted study should facilitate characterization of meloxicam pharmacokinetics in pediatric patients.

Study 2: This study should be a three-month or more, randomized, double-blind, three-arm (two dosages, one active control), efficacy/safety and dose-response trial,

followed by an extension of at least 12 weeks. The JRA study doses should correspond to the efficacious doses in adult RA. 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 in pediatric clinical studies. Prior use of the chosen comparator should be addressed. Inclusion of 5% to 10% of patients with systemic course JRA is recommended.

Study 3: This study should be a three-month or more, randomized, double blind, active comparator controlled, efficacy and safety study in patients with polyarticular and pauciarticular JRA. Inclusion of 5% to 10% of patients with systemic course JRA is recommended.

Patients must be allowed to continue receiving standard-of-care therapy and concomitant medications as indicated in the eligibility criteria.

Clinical Endpoints:

Study 1: The primary PK analysis should attempt to include all the patients in the study (with determination of parameters such as AUC, Cmax, Cmin, Tmax and CL/F, as applicable). The data from the conducted study should be compared with published meloxicam single and multiple dose pharmacokinetic studies.

Studies 2 & 3: The primary efficacy endpoint should be the JRA 30 Definition of Improvement ≥ 30% (JRA DOI 30). The assessment of secondary efficacy variables is encouraged, e.g., the proportion of patients with improvement from baseline in the parent/patient overall assessment of well-being, the parent/patient's global assessment of pain, and the individual components of the JRA DOI 30 core set.

Drug Information:

- **Route of administration:** oral
- **Formulation:** age appropriate formulation.
- **Regimen:** to be determined

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 JRA patients (e.g. iritis/uveitis for pauciarticular disease, coagulopathy events for systemic JRA), 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, cardiovascular, 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 safety data on systemic course JRA 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, body-weight, gender, and race on meloxicam pharmacokinetic parameters should be explored. Information derived from both single and multiple dose studies (including published literature) should be utilized for full characterization of meloxicam pharmacokinetics in the pediatric population. The meloxicam pharmacokinetics parameter determined from pediatric patients should also be compared to either an adult rheumatoid arthritis control group or historical pharmacokinetic data in patients with adult rheumatoid arthritis. If employed, a historical group should be pre-specified and justified.

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

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

Study 1: Analyses of the PK parameters (such as, Cmax, Tmax, AUC, and T1/2) should include descriptive summary statistics as well as evaluation of age, body-weight, gender and race effects.

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 meloxicam doses and the active control, and one difference test comparing the two meloxicam dosages used. Alternatively, demonstrate superiority of meloxicam to the active comparator. Multiplicity issues should be considered. Safety data should be analyzed by descriptive statistics. Concomitant use of indicated standard therapy should be incorporated into the analysis of efficacy and safety.

Labeling that may result from the studies:

Information collected from this study should permit the determination of appropriate labeling for the use of meloxicam in pauciarticular and/or polyarticular type JRA in pediatric patients 2 years to < 17 years of age.

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. In addition, the

reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Include other information as appropriate. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

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 March 01, 2005. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated. 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 (NDA) or 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

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 in the pediatric population.

If you have any questions, call Barbara Gould, Project Manager, at 301 827-2506.

Sincerely,

Brian E. Harvey, M.D., Ph.D.
Deputy 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/

Brian Harvey
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