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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-905

MAR 30 1999

Hoechst Marion Roussel, Inc.
Attention: J. Michael Nicholas, Ph.D.
Director, U.S. Drug Regulatory Affairs
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Dear Dr. Nicholas:

To obtain needed pediatric information on **Arava® (leflunomide tablets)** for the treatment of juvenile rheumatoid arthritis (JRA), the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following study(ies):

Study(ies) of leflunomide dosing with at least 120 pediatric patients between approximately six and 16 years of age with JRA (at least one third of whom are less than twelve years of age) treated for at least six months. Enrolled patients should include male and non-pregnant female pediatric patients, with clinical diagnosis of polyarticular course JRA as defined by the American Rheumatism Association criteria. The primary objectives of the study(ies) should be to:

1. Assess the efficacy in treating polyarticular course JRA as measured by a controlled comparison over at least 3 months of therapy
2. Evaluate the steady-state pharmacokinetic parameters,
3. Evaluate the safety, tolerability profile and the durability of efficacy over six months of therapy.

Information collected in the study(ies) should permit the determination of appropriate therapeutic dose and appropriate labeling instructions. The objectives identified above could be collected in one to three studies.

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.

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 (RA) patients.

There should be prompt evaluation of pharmacokinetic samples from early study entrants to ensure design assumptions are appropriate.

Clinical evaluations should include clinical safety (as assessed by laboratory results and physical examination) and clinical response (as assessed by the JRA core set responder index).

Statistical analyses should include baseline demographics (age, sex, weight, race, etc.) summarized by center and overall; clinical response; incidence rates of adverse events and premature withdrawals; changes from baseline in laboratory values, vital signs and body weight. All analyses should be summarized and where appropriate analyzed by paired t-test; with the results of statistical tests declared significant if $p < 0.05$ (two-tailed comparison).

Safety data should be tabulated including serious and other adverse reactions, deaths, withdrawals and drop-outs. Clinical data should be explored for factors (e.g., dose, baseline severity) that may affect clinical response.

For the pharmacokinetic portion of the study(ies), in addition to the primary analysis, a comparison to pharmacokinetic parameters for adult RA patients should be performed and a covariate analysis performed across gender, age and body weight in the target population should be included.

At the completion of the study(ies), full study reports providing the analyses outlined in this request should be provided, with full analysis, assessment, and interpretation. The report(s) must be submitted by November 30, 2001. Any plans for obtaining ongoing follow-up information should also be included in this submission.

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 note that we recommend that you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act)*, with FDA before developing pediatric protocols. 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 this study(ies) should be submitted as a supplement to your approved Arava NDA 20-905 with the proposed labeling you believe would be warranted based on the data derived from this study(ies). When submitting the reports of this pediatric study, 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 mail/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 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, please contact Ms. Sandra Cook, Project Manager, at (301) 827-2050.

Sincerely yours,

Robert J DeLap 3/30/1999

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: NDA 20-905
HFD-550/Div. Files
HFD-550/CSO/Cook Sue 3/17/99 cons 3/29/99
HFD-550/PedRep/Ludwig/Dunbar 3/19/99
HFD-550/DepDir/Hyde JC for 3 25-99
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HFD-550/MO/Johnson 3/29/99
HFD-550/MO/Witter
HFD-880/Biopharm/Bashaw 3/23/99
HFD-105/DeLap
HFD-105/ADRA/Walling
HFD-600/Office of Generic Drugs
HFD-104/Murphy
HFD-2/Lumpkin
HFD-6/KRoberts

Drafted by: Chambers/March 9, 1999
Revised: Chambers 3/18/99

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PEDIATRIC WRITTEN REQUEST LETTER (PWR)