DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537
NDA 19-847
NDA 19-857
NDA 20-780
NDA 21-473
NDA 21-554

Andrew S. Verderame
Director, Regulatory Affairs
Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516

Dear Mr. Verderame:

Reference is made to your Proposed Pediatric Study Request submitted August 14, 1998, received August 17, 1998 to NDA 19-537 CIPRO® (ciprofloxacin hydrochloride) Tablets, NDA 19-847 CIPRO® I.V. (1% ciprofloxacin solution), NDA 19-857 CIPRO® I.V. (0.2% ciprofloxacin in 5% dextrose), NDA 19-858 CIPRO® I.V. (1% ciprofloxacin in 0.9% NaCl) and NDA 20-780 CIPRO® (Ciprofloxacin) Oral Suspension. Reference is also made to the Written Request letters dated May 12, 1999 and October 1, 2001.

To determine if information relating to the use of CIPRO® (ciprofloxacin IV, oral tablets, and suspension) in the pediatric population may produce health benefits in that population, 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 (the Act) to submit information for the following types of studies. This Written Request will supersede the Written Request dated October 1, 2001.

In the design of these studies, consideration is given to the fact that systemic use of ciprofloxacin has been associated with arthropathy in juvenile animals and there is a need to develop a safety database to better understand the safety profile of this drug in the pediatric population. There is a need to develop information on the incidence of serious adverse events in this population, as well as gain additional safety data in pediatric patients with complicated urinary tract infection (cUTI) and/or acute pyelonephritis. In particular there is a need to determine if pediatric use of ciprofloxacin may predispose to musculoskeletal abnormalities following exposure.

Type of studies:
(Study 1) A prospective, randomized, multicenter, comparative, investigator-blinded study in the pediatric population 1 year of age to less than 17 years of age with complicated urinary tract infection (cUTI) and/or acute pyelonephritis should be conducted. This study should compare ciprofloxacin (orally, intravenously or sequentially) with an established active nonquinolone antimicrobial control.

(Study 2) A pharmacokinetic analysis of varied doses of ciprofloxacin in pediatric patients enrolled in Study 1 with cUTI and/or acute pyelonephritis and from pediatric patients with various infection diagnoses should be conducted.

(Study 3) A prospective, multicenter, active-controlled pediatric study to evaluate long term (up to 5 years) musculoskeletal and neurological system health following ciprofloxacin or nonquinolone antimicrobial treatment in pediatric patients. The requirement for safety data beyond one year follow-up in patients who did not experience any musculoskeletal adverse events may be reassessed as additional information regarding pediatric quinolone safety becomes available.

Indication to be studied (i.e., objective of each study):
(Study 1) The primary objective should be to provide comparative safety adverse event data (including arthropathy incidence) for ciprofloxacin and an appropriate control group in pediatric patients with cUTI and/or acute pyelonephritis. The secondary objectives should evaluate the efficacy of ciprofloxacin in cUTI and/or acute pyelonephritis. Study treatments should include ciprofloxacin [purely i.v., sequential (i.v. to oral), or purely oral] or antimicrobial controls [purely i.v., sequential (i.v. to oral), or purely oral] and should enroll approximately 300 patients in each treatment arm.

(Study 2) The primary objective should be to evaluate the pharmacokinetics of varied doses of ciprofloxacin in the pediatric population and with various infection diagnoses, including those with cUTI and/or acute pyelonephritis, that will allow development of appropriate dosing recommendations in the pediatric population.

(Study 3) The primary objective should be to detect serious adverse events, including musculoskeletal and neurological, by ensuring enrollment of approximately 500 non-cystic fibrosis pediatric patients treated with ciprofloxacin and approximately 500 non-cystic fibrosis pediatric patients treated with a nonquinolone antimicrobial for an infectious process. This study should be a prospective, multicenter, pediatric study that separately evaluates the musculoskeletal and neurological system health in pediatric patients treated with either ciprofloxacin or a nonquinolone antimicrobial. The dose, formulation (IV solution, oral suspension or oral tablet), route of administration, and time of switch (from IV to oral therapy) should be selected based on the clinical judgement of the treating physician.

Age groups in which study will be performed:
(Studies 1 and 2) The following age groups should be studied: ≥ 12 months but < 24 months, ≥ 2 through < 6 years, ≥ 6 through < 12 years, and ≥ 12 through < 17 years. A minimum of 20% of the study population should consist of patients ≤ 5 years.

(Study 3) The following age groups should be studied: ≥ 2 months but < 24 months, ≥ 2 through < 6 years, ≥ 6 through < 12 years, and ≥ 12 through < 17 years. A minimum of 20% of the study population should consist of patients ≤ 5 years.

Number of patients to be studied or power of study to be achieved:
(Study 1) A minimum of 600 patients randomized 1:1 with at least 300 patients per arm should be enrolled, with approximately 275 patients per treatment arm having 1-year follow-up data available by July, 2003.

(Study 2) Blood samples from a minimum of 100 ciprofloxacin-treated patients from Study 1 will be analyzed and reported.

(Study 3) For the purpose of completing the entire study, approximately 500 ciprofloxacin-treated patients should have been enrolled. In addition, approximately 500 nonquinolone antimicrobial-treated patients should have been enrolled. Approximately 450 patients should have 1-year follow-up by July 2003 (approximately 225 pediatric patients per study arm).

Study endpoints and timing of assessments:
(Study 1) The primary [safety] endpoint should be the development of any adverse event with particular attention to musculoskeletal and CNS events that occur during treatment or within 1 year following ciprofloxacin or control drug

exposure. Clinical evaluations (gait/joint examination) should be performed at least once during therapy and at the test of cure visit, 1 month, and 1 year following ciprofloxacin or control drug exposure. Special emphasis should be placed on the evaluation of adverse event rates. Gait/joint examinations should be performed by either rheumatologists or trained physical therapists experienced in musculoskeletal examinations. Telephone calls should be conducted at approximately six and nine months following exposure to assess musculoskeletal and neurologic complaints. Pediatric rheumatologic follow-up should be obtained if any signs or symptoms suggestive of arthropathy develop. Patients who develop joint effusions should have joint fluid evaluations. Patients that develop arthropathy, regardless of the degree of severity, should have a MRI (or other appropriate imaging technique) of the affected joint, as deemed clinically necessary by the treating physician and/or rheumotologist. Efficacy evaluations including clinical and microbiological assessments of cUTI and/or acute pyelonephritis should also be performed at approximately 1 week and 1 month following ciprofloxacin or control drug exposure. Case definitions pertaining to musculoskeletal adverse events and causality attributions should be developed. Such case definitions should be applied to individual adverse events by an independent safety board who will be blinded as to treatment group.

(Study 2) Pharmacokinetic data should provide dosing administration guidance in the pediatric population. We recommend using a population pharmacokinetic approach that uses data from several studies, in addition to that from Study 1.

(Study 3) The primary [safety] endpoint should be the development of any serious adverse event and any musculoskeletal or neurologic adverse event that occurs during or following the administration of ciprofloxacin or nonquinolone comparator drug therapy. The outcome of all adverse events should be identified and the severity of musculoskeletal and neurologic adverse events should be characterized. Patients should receive two structured assessments for general, neurological and musculoskeletal safety, i.e., evaluations of the joints (especially all weight-bearing joints) and gait. These should be conducted pre-therapy or up to 72 hours after the initiation of therapy and at approximately one month following exposure. In the pre-pubescent or pubescent pediatric patient, a trained interviewer should perform an assessment at the end of the first year post-exposure and annually thereafter for up to 5 years. In the post-pubescent pediatric patient, a trained interviewer should perform an assessment at the end of the first year post-exposure. Patients who experience a musculoskeletal adverse event should be followed for 5 years, regardless of the stage of pubescence. A final report which includes the five year follow-up data will be provided to the Agency by December 15, 2008. The requirement for safety data beyond one year follow-up in patients who did not experience any musculoskeletal adverse events may be reassessed as additional information regarding pediatric quinolone safety becomes available.

Study evaluations:
(Study 1) Evaluations should be made prior to exposure, during treatment, and at the test of cure visit, l month, and 1 year following ciprofloxacin or control drug exposure.

(Study 2) Covariates (including age, body weight, renal function, etc.) that may affect the pharmacokinetics of ciprofloxacin in this patient population should be evaluated. The pharmacokinetics of ciprofloxacin in the pediatric population should be determined.

(Study 3) Evaluations for pre-pubescent or pubescent pediatric patients should be made at baseline, 1 month, and 1 year following treatment and yearly thereafter up to a period of 5 years following antibiotic treatment. Evaluation for post-pubescent pediatric patients should be made a baseline, and approximately 1 month, and 1 year following antibiotic treatment. Attempts should be made to periodically follow any pediatric patient who develops musculoskeletal adverse events preferably for a period of 5 years, regardless of the pubertal stage. The Division anticipates that data will be provided for at least 50% of those patients who were to be followed for 5 years. A reason for the loss to follow-up should accompany the report of any patient who is not followed for the appropriate time period. A final report which includes the five year followup data will be provided to the Agency by December 15, 2008. The requirement for safety data beyond one year follow-up in patients who did not experience any musculoskeletal adverse events may be

reassessed as additional information regarding pediatric quinolone safety becomes available.

Drug information:
(Study 1)
- *Dosage forms:* I.V. solution, oral tablet, or oral suspension.
- *Regimen:* ciprofloxacin and appropriate comparator regimens should be used and doses should be adjusted depending on the severity of cUTI at baseline.
- *Route of administration:* intravenous or oral
- *Formulation:* I.V. solution, oral tablet, or oral suspension

(Study 2)
- *Dosage forms:* I.V. solution, oral tablet, or oral suspension.
- *Regimen:* any ciprofloxacin regimen.
- *Route of administration:* intravenous or oral
- *Formulation:* I.V. solution, oral tablet, or oral suspension

(Study 3)
- *Dosage forms:* I.V. solution, oral tablet, or oral suspension.
- *Regimen:* any ciprofloxacin or non-quinolone antibiotic regimen
- *Route of administration:* intravenous or oral
- *Formulation:* I.V. solution, oral tablet, or oral suspension

Safety concerns:
(Studies 1, 2 and 3) The development of arthropathy, arthritis, or neurologic events is the major safety concern.

Statistical information of the study:
(Study 1) The study should enroll at least 300 patients per arm.

(Study 2) The study should include plasma concentrations from at least 100 ciprofloxacin-treated patients from Study 1.

(Study 3) The study should enroll at least 500 ciprofloxacin-treated patients and approximately 500 nonquinolone antimicrobial-treated patients.

Statistical analyses of data to be performed:
(Study 1) Comparative descriptive statistical analyses should be performed on all adverse event rates between treatment arms. Although demonstration of efficacy is a secondary endpoint of the study, comparative statistical analyses should be used for clinical and bacteriological assessments.

(Study 2) Pharmacokinetic analyses should be performed to determine pharmacokinetic parameters in the pediatric population that will allow for adequate dosing recommendations. In these analyses, age should be treated as a continuous variable and as a categorical variable.

(Study 3) Adverse event rates should be calculated for all events. Ninety-five percent confidence intervals should be calculated for the rates of all musculoskeletal events and neurological events for events occurring through the 28 to 42 days post-therapy visit, and separately for events occurring after this visit through the one year follow-up visit and all appropriate follow-up visits. Rates and confidence intervals will be generated separately for ciprofloxacin-treated patients and nonquinolone antimicrobial-treated pediatric patients.

Lifetime tables should be provided to present cumulative incidence rates for events occurring at these time points in the

ciprofloxacin and nonquinolone comparator groups, for all patients as well as stratified by age groups.

Labeling that may result from the studies:
These studies will provide safety information including the incidence of musculoskeletal adverse events for ciprofloxacin in pediatric patients. Information regarding the proper dose for safe and efficacious use in pediatric patients with serious infections may also be provided, if appropriate.

Format of report to be submitted to the Agency:
Full study reports of requested studies 1 (enrollment of at least 300 patients per study arm) and 2 (including plasma concentrations from at least 100 ciprofloxacin-treated patients from Study 1), including full analysis, assessment, and interpretation, should be submitted in the usual format. As an alternative, you may submit an abbreviated study report along with all data in electronic form, with a case report form annotated with the names of the SAS variables used for each blank on the form.

For the purposes of this written request, a study report should be submitted for study 3 that includes the results of safety analyses for approximately 500 patients ciprofloxacin-treated patients and approximately 500 nonquinolone antimicrobial-treated patients. At least 225 ciprofloxacin-treated patients and 225 nonquinolone antimicrobial-treated patients should have a one year follow-up.

Timeframe:
Study reports for the studies described above should be submitted by September 30, 2003. Please keep in mind that pediatric exclusivity attaches 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.

Animal Studies: Post-Dosing Arthrotoxicity Susceptibility Study
An animal study designed to evaluate the potential for ciprofloxacin to cause latent arthrotoxicity in the juvenile dog model should be performed. Juvenile dogs should be dosed for a period of 7 to 14 days at three discrete dose levels (high, middle, and low) of ciprofloxacin. A no-treatment control group should be included. The study design should include the sacrifice of 3 dogs from both sexes per dose level at 24 hours following the final dose and at 6 to 9 months of age. Gross pathology, histopathology, and electron microscopic analysis of chondrocytes should evaluate all weight-bearing joints and growth plates (where present) from each dog.

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. We recommend you seek a written agreement with FDA before developing pediatric studies. 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 supplement to your approved NDA, new drug application, or an amendment to your pending application 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 in the pediatric population.

If you have any questions, call Jouhayna Saliba, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Mark Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
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/

Mark Goldberger

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