HFD-104/Murphy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

**NDA 19-537 CIPRO ® 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)**
**NDA 20-780 CIPRO ® (Ciprofloxacin) Oral Suspension**

MAY 12 1999

Andrew S. Verderame
Associate Director, Regulatory Affairs
Bayer Corporation
400 Morgan Lane
West Haven, CT 06416-4175

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.

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.

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 quality safety database to better understand the safety risks of this drug in the pediatric population. There is a need to develop information on the true incidence of rare, serious adverse events in this population, including persistent and disabling arthropathy 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 will predispose to musculoskeletal abnormalities 5 to 10 years following exposure. Although this written request only requires up to 3 years of follow-up safety data, it is expected that long term follow-up (5 to 10 years) will be acquired.

***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. The study should compare ciprofloxacin (orally, intravenously or sequentially) with an established active nonquinolone antimicrobial control.

(Study 2) A pharmacokinetic study of varied doses of ciprofloxacin using patients with cUTI and/or acute pyelonephritis should be conducted. This study should use the same patients as enrolled in study 1.

(Study 3) A prospective, multicenter, pediatric study to evaluate long-term musculoskeletal and neurological system health.

***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].

(Study 2) The primary objective should be to evaluate the pharmacokinetics of varied doses of ciprofloxacin in the pediatric population who have cUTI and/or acute pyelonephritis in selected age groups. A secondary objective should be to evaluate the pharmacokinetics among patients with renal insufficiency within the study population. Pharmacokinetic data should be generated such that appropriate dosing recommendations in the pediatric populations can be provided.

(Study 3) The primary objective should be to detect serious adverse event rates in the range of 1 in 1000 by ensuring complete follow-up in at least 3,000 non-cystic fibrosis pediatric patients in whom ciprofloxacin has been initiated for therapy of an infectious process. This study should be a prospective, multicenter, pediatric study that evaluates the long-term musculoskeletal and neurological system health in this population. 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: $\geq$ 12 months but < 24 months, $\geq$ 2 through < 6 years, $\geq$ 6 through < 12 years, and $\geq$ 12 through < 17 years. A minimum of 20% of the study population should consist of patients $\leq$ 5 years of age and a minimum of 10% should be less than 2 years.

(Study 3) The following age groups should be studied: $\geq$ 2 months but < 24 months, $\geq$ 2 through < 6 years, $\geq$ 6 years through < 12 years, and $\geq$ 12 through < 17 years. A minimum of 20% of the study population should consist of patients $\leq$ 5 years of age and a minimum of 10% should be less than 2 years of age.

***Number of patients to be studied or power of study to be achieved:***
(Studies 1 and 2) A minimum of 400 patients randomized 1:1 with at least 200 patients per arm should be enrolled.

(Study 3) For the purpose of completing the entire study, 3,000 patients should have been followed-up for 5 years (age ≥ 2 months to < 6 years) or 10 years (age ≥ 6 years to < 17 years). However, to satisfy the requirements of this written request, at least 2,900 patients should have been followed-up by September 30, 2003 for the following durations: 3 years (at least 900 patients), 2 years (at least 1000 patients) and 1 year (at least 1000 patients). A minimum of 20% of this population should consist of patients < 6 years of age and a minimum of 10% should be < 2 years of age.

***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 *(including gait/joint examination) should be performed at least once during therapy and at* approximately 1 week, 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.* 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.

(Study 2) Pharmacokinetic data should provide meaningful dosing administration guidance in the pediatric population. Dosing schedules for patients with acute or chronic renal insufficiency should also be developed and evaluated in this study. We recommend using a population pharmacokinetic approach that uses pre-determined sparse blood sample-times (at least 1 sample per subject) among evaluable subjects in study 1. The optimal sample-times should be staggered throughout the dosing interval. Efforts should be made to assign adequate numbers of patients per sampling time point. Additional samples (up to a total of 4 samples per patient) from at least 15 patients between the ages of 1 and 5 should also be collected.

(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. The reversibility 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 and at approximately one month following exposure. At the end of the first year post-exposure

and, thereafter, a trained interviewer should perform annual assessments for up to five years (for patients ≥ 6 years of age) or ten years (for patients < 6 years of age). Pediatric rheumatology follow-up should be obtained if any signs or symptoms suggestive of arthropathy develop. Case definitions should be developed to characterize the severity and duration of arthropathy. Patients who develop joint effusions should have joint fluid evaluations. Patients that develop arthropathy, regardless of the degree of severity, should undergo MRI (or other appropriate imaging technique) of the affected joint.

***Study evaluations:***
(Study 1) Evaluations should be made prior to exposure, during treatment, and at approximately 1 week, 1 month, and 1 year following ciprofloxacin or control drug exposure.

(Study 2) Covariates (including age, body weight, degree of renal impairment, etc.) that may affect the pharmacokinetics of ciprofloxacin in this patient population should be evaluated. Sparse sampling (at least 1 sample per subject) should be used to determine the pharmacokinetics of ciprofloxacin in a pediatric population.

(Study 3) Evaluations should be made at baseline, 1 month following treatment and yearly thereafter until the end of the study (5 years for patients ≥ 6 years and 10 years for patients < 6 years of age).

***Drug information:***
(Studies 1 and 2)
- *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. Dosing regimens for renal insufficiency should be also be developed and evaluated.
- *Route of administration*: intravenous or oral
- *Formulation*: solution, oral tablet, or oral suspension

(Study 3)
- *Dosage forms*: I.V. solution, oral tablet, or oral suspension
- *Regimen*: any regimen
- *Route of administration*: intravenous or oral
- *Formulation*: 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 and power of the study:***
(Study 1) The study should include at least 200 patients per arm. Using an arthropathy incidence rate of 1.5%, a delta of 3.5%, and a one-sided alpha = 0.025, a total of at least 400 patients should provide an 88% power for rejection of the null hypothesis of inequivalence.

(Study 2) The study should determine ciprofloxacin blood levels in a minimum of 200 ciprofloxacin-treated patients.

(Study 3) The study should follow-up at least 3,000 ciprofloxacin patients to have a 95% probability of seeing at least one adverse event (1:1000) using a binomial distribution. Approximately 80% (2,400 patients $\geq$ 6 years of age) should be followed for at least 5 years and approximately 20% (600 patients < 6 years of age) should be followed for at least 10 years.

***Statistical analyses of data to be performed:***
(Study 1) Comparative 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 with cUTI and/or acute pyelonephritis that will allow for adequate dosing recommendations. In these analyses, age should be treated as a continuous variable instead of a categorical variable.

(Study 3) Adverse event rates and 95% confidence intervals should be calculated for all events including musculoskeletal events and CNS events of differing severity. This should be done for both events that occur during ciprofloxacin exposure and events occurring after ciprofloxacin exposure.

***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 will also be provided.

***Format of report to be submitted to the Agency:*** Full study reports of requested studies 1 and 2, 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 at least 2,900 patients. These patients should have had the following follow-up durations: 3 years (at least 900 patients), 2 years (at least 1000 patients) and 1 year (at least 1000 patients).

***Time frame:*** Study reports for the studies described above should be submitted by September 30, 2003.

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, please contact Mary Dempsey, Regulatory Project Manager, at (301) 827-2127.

Sincerely yours,

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Archival NDA 19-537
NDA 19-847
NDA 19-857
NDA 19-858
NDA 20-780
NDA 20-805
NDA 20-369
NDA 19-992
HFD-590/division file
HFD-520/division file
HFD-550/division file
HFD-590/PM/MDempsey
HFD-104/Acting Office Director/S Kweder
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts
HFD-590/DepDirector/RAlbrecht
HFD-590/MTL/RHopkins
HFD-590/MTL/BLeissa
HFD-590/MTL/MCavaillé-Coll
HFD-590/StatTL/NSilliman
HFD-590/BiopharmTL/FAjayi
HFD-736/DivDir/ERodriguez
HFD-736/MO/AVega

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Final: 5/12/99
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PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)