Division of Special Pathogen and Immunologic Drug Products

Summary of Clinical Review of Studies Submitted in Response to a Pediatric Written Request

Applications: 19-537/S-049, ciprofloxacin tablets
20-780/S-013, ciprofloxacin oral suspension
19-847/S-027, ciprofloxacin IV 10 mg/mL
19-857/S-031, ciprofloxacin IV 5% dextrose

Applicant: Bayer Corporation, Pharmaceutical Division
400 Morgan Lane
West Haven, Connecticut 06516

Drug Name Established: Ciprofloxacin

Proprietary: Cipro®

Route: Oral or IV

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BACKGROUND

Ciprofloxacin (Cipro®) is an antibacterial fluoroquinolone. The oral tablets were approved in October 1987, the intravenous formulations were approved in December 1990, and the oral suspension was approved in September 1997. Ciprofloxacin is approved for the following indications in adults: acute sinusitis, bone and joint infections, chronic bacterial prostatitis, complicated intra-abdominal infections, infectious diarrhea, lower respiratory tract infections, skin and skin structure infections, typhoid fever (enteric fever), uncomplicated cervical and urethral gonorrhea, and urinary tract infections. In August 2000, ciprofloxacin was approved for inhalational anthrax (post-exposure) in adults and children.

The current supplemental applications were submitted in response to a Pediatric Exclusivity Written Request (WR) originally issued May 12, 1999, amended October 1, 2001, and a final amendment was dated September 23, 2003. The applications contain the results of two clinical trials in pediatric patients, a population pharmacokinetic analysis, and an animal toxicology study. The applicant is requesting to update the PRECAUTIONS, Pediatric Use and ANIMAL PHARMACOLOGY sections of the labeling.

Currently, ciprofloxacin, like other quinolone drug products, carries a WARNING, printed in all capital letters, that states:

> **"Safety and effectiveness of ciprofloxacin in pediatric patients and adolescents (less than 18 years of age), except for use in inhalational anthrax (post-exposure)…have not been established"**

This statement is included because the quinolones cause arthropathy in most animal species tested. The ciprofloxacin labeling further states,

> "The oral administration of ciprofloxacin caused lameness in immature dogs. Histological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species."

As a result of these preclinical findings, the Agency has brought the issue of quinolone drug development in pediatrics to the Anti-Infective Advisory Committee on three occasions:

> November 1989 – The committee recommended that pediatric studies could be undertaken in patients with cancer, cystic fibrosis, and sickle cell disease patients with Salmonella infections.
>
> July 1993 – The indications for consideration were: cystic fibrosis, complicated urinary tract infections, chronic suppurative otitis media, pseudomonal osteomyelitis, invasive enteritis due to multiply-resistant pathogens, and febrile neutropenia. An ongoing cystic fibrosis study was discussed. The committee recommended that pediatric studies be limited to certain special disease entities where the products potentially offer significant advantage.
>
> November 1997 – The committee recommended that pediatric studies could be approached incrementally, with more serious indications being studied first. Suggested indications included meningitis, pneumonia, sepsis, bacteremia, complicated urinary

tract infections, osteomyelitis, chronic suppurative otitis media, external otitis with tissue invasion, recurrent and severe otitis media, and treatment failure of acute otitis media.

Clinical Trials

Study 100169

This was a prospective, randomized, double-blind, active-controlled, parallel group, multinational, multicenter pediatric clinical trial. Patients from 1 year to < 17 years diagnosed with complicated urinary tract infection (cUTI) or pyelonephritis were enrolled. Patients were stratified prior to randomization based on whether, in the opinion of the clinical investigator; intravenous (IV) therapy was initially warranted. Patients were then randomized to receive either ciprofloxacin or comparator antibiotics. In the first stratum, ciprofloxacin oral suspension was compared to the comparator regimens of oral cefixime or trimethoprim/sulfamethoxazole (TMP/SMX) [in Canada only]. In the second stratum ciprofloxacin (IV or IV followed by oral suspension) was compared to one of the following comparator regimens: IV ceftazidime; IV ceftazidime followed by oral cefixime; and sequential IV ceftazidime to oral TMP/SMX [in Canada only].

The primary objective of this study was to determine the musculoskeletal safety, including effects on joints, cartilage, tendons, and ligaments, of ciprofloxacin in pediatric patients with cUTI or pyelonephritis. The secondary objective was to assess neurological safety.

A patient's clinical and microbiological response to ciprofloxacin or comparator regimen, evaluated 5 to 9 days following the end of therapy (i.e., the Test-of-Cure visit) were additional objectives of this trial.

The daily dose of ciprofloxacin administered as therapy in this trial was adjusted according to the child's body weight and conformed to a detailed set of dosing guidelines shown in the tables below. Pediatric patients with moderate to severe renal insufficiency (i.e., creatinine clearance of < 60 mL/min/1.73m^2) were excluded.

Definitions for mild, mild-to-moderate, moderate-to-severe and severe cUTI and pyelonephritis that formed the basis for the dosing of ciprofloxacin IV and oral therapy were determined by the physician.

Ciprofloxacin IV Dosing*
Stratum II

Pediatric dose	Dose Regimen Suitability Based Upon Severity of Infection at Presentation
6 mg/kg every 8 hours (total daily dose 18 mg/kg)	moderate cUTI or pyelonephritis
10 mg/kg every 8 hours (total daily dose 30 mg/kg)	severe cUTI or pyelonephritis

* Pediatric IV ciprofloxacin doses of 400 mg every 8 hours (i.e., total IV daily dose 1200 mg) were maximum doses in this study and were not to be exceeded, even in children weighing over 51 kg.

Ciprofloxacin Oral Suspension Dosing*
Stratum I and Stratum II

Pediatric dose	Dose Regimen Suitability Based Upon Severity of Infection at Presentation
10 mg/kg every 12 hours (total daily dose 20 mg/kg)	Mild to moderate cUTI or pyelonephritis
15 mg/kg every 12 hours (total daily dose 30 mg/kg)	Moderate to severe cUTI or pyelonephritis
20 mg/kg every 12 hours (total daily dose 40 mg/kg)	severe cUTI or pyelonephritis

* Pediatric ciprofloxacin doses of 750 mg every 12 hours orally (i.e., total oral daily dose 1500 mg) were maximum doses in this study and were not to be exceeded, even in children weighing over 51 kg.

The total duration of therapy, was determined by the physician, but ranged between 10 and 21 days, inclusive. Investigators were to consider the patient's age, age-adjusted renal function, and extent and severity of documented structural/anatomic or functional genitourinary tract abnormalities when projecting an intended duration of study drug therapy required to achieve clinical cure and bacteriological eradication.

A total of 689 patients ranging in age from 1 year to < 17 years were enrolled in this study. Of these, 684 (99.3%; 335 ciprofloxacin, 349 comparator) received at least 1 dose of study drug and were valid for the analysis of safety. A total of 442 patients (64%; 211 ciprofloxacin, 231 comparator) were considered valid for efficacy (i.e., Per Protocol population). Of these, 256 (58%) had pyelonephritis and 186 (42%) had cUTI. The mean duration of treatment was 11 $\pm$ 4 days.

Study 100201 – Data up to one-year follow-up

This was a prospective, open label, multi-center North American pediatric clinical observational study to assess long-term musculoskeletal and neurological system health in infants and younger children (i.e., ≤ 6 years of age at study entry) for up to 5 years post-exposure to ciprofloxacin or a non-quinolone antibiotic for prepubescent and pubescent children and for 1 year post-exposure to ciprofloxacin or non-quinolone antibiotic for post-pubescent children.

Patients in the age range of 2 months through 16 years of age were eligible for enrollment in the study. Low-risk febrile patients with neutropenia during cancer chemotherapy could be enrolled provided their neutropenia (≥ 500 cells per mm^3) was expected to resolve within 10 days after the onset of fever.

The decision to treat with ciprofloxacin or a non-quinolone antibiotic was made prior to enrollment in the study and was based on the particular infection, medical history and the clinical evaluation by the prescribing physician. After the investigator determined that a particular infant or child with an eligible infection was suitable for treatment with ciprofloxacin or a non-quinolone antibiotic, the selection of study unit dose, total daily dose, duration of therapy, route of administration, and formulation (i.e., IV, oral suspension, or oral tablets) was left to the discretion of the investigator. In general, ciprofloxacin or non-quinolone antibiotic therapy was to be administered for a minimum duration of 7 days and a maximum duration of 21 days.

As requested in the pediatric WR, safety results from the first year post-treatment were provided for 487 ciprofloxacin-treated patients and 507 non-quinolone control patients valid for safety analysis. The mean duration of treatment was 12 ± 8 days (range 1 to 88 days).

Population Pharmacokinetic Analysis

A pharmacokinetic analysis of varied doses of ciprofloxacin in pediatric patients enrolled in Study 100169 with cUTI or acute pyelonephritis and from pediatric patients with various infection diagnoses was conducted. The primary objective was to evaluate the pharmacokinetics of varied doses of ciprofloxacin in a pediatric population with various infection diagnoses, including those with cUTI or acute pyelonephritis, to allow the development of appropriate dosing recommendations in the pediatric population.

See summary by Dakshina Chilukuri, PhD, Clinical Pharmacology/Biopharmaceutics Reviewer, in HFD-590 (DSPIDP).

Animal Toxicology Study

The animal study was designed to evaluate the potential for ciprofloxacin to cause latent arthrotoxicity in the juvenile dog model. Juvenile dogs were 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 was also included. Sacrifice of 3 male and 3 female dogs per dose level occurred at 24 hours following the final dose in the first cohort and at 6 to 9 months of age (recovery) in the second cohort. Gross pathology, histopathology, and electron microscopic analysis of chondrocytes evaluated all weight-bearing joints and growth plates (where present) in each dog.

SAFETY

I. Study 100169

The primary endpoint of the study was the evaluation of arthropathy at six weeks of follow-up (i.e., occurring by Day +42). An Independent Pediatric Safety Committee (IPSC) reviewed patient records of all cases of musculoskeletal system events, abnormal gait or joint appearance (baseline and treatment emergent), and selected other events. All cases were reviewed in a blinded fashion, and were judged as either having no evidence of clinically diagnosed arthropathy, or as having at least possible evidence of arthropathy. Arthropathy was broadly defined as any condition affecting a joint or periarticular tissue that may have been temporary or permanent. This definition included events such as bursitis, enthesitis (inflammation of the muscular or tendinous attachment to the bone) and tendonitis.

Arthropathy occurred more frequently in patients who received ciprofloxacin than the comparator and was defined as any condition affecting a joint or periarticular tissue that may have been temporary or permanent (including bursitis, inflammation of the muscular or tendinous attachment to the bone, and tendonitis). The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Arthropathy, as shown in Table 1, was seen in 9.3% (31/335) of ciprofloxacin patients versus 6% (21/349) of comparator patients at 6 weeks. All musculoskeletal events occurring by 6 weeks resolved, usually within 30 days of end of treatment. The rates were 13.7% and 9.5%, respectively, at 1 year. Arthropathy occurred more frequently in patients treated with ciprofloxacin than control, regardless of whether they received IV or oral drug. Ciprofloxacin patients were more likely to report more than

one event and on more than one occasion compared to control patients (37% [17/46] versus 24% [8/33]).

Of the 46 patients with arthropathy in the ciprofloxacin arm, radiological testing was reported for 5 patients. Results of all tests were negative and included: X-ray of hip for abnormal gait, lumbosacral films for lumbar pain, X-ray of hips and spinal cord for back pain and thoracic spine pain, X-ray of ankle, knee, and feet for growing pains, and MRI for ankle pain and swelling. Of the 33 comparator patients, 1 had an X-ray for ankle pain and the results were negative.

TABLE 1
Arthropathy Rate up to 1 Year of Follow-up in Patients Valid for Safety

	Ciprofloxacin (N=335)	Comparator (N=349)
Arthropathy rate at 6 weeks of follow-up	**31 (9.3%)**	**21 (6.0%)**
95% Confidence Interval*	(-0.8%, +7.2%)	
Cumulative Arthropathy rate at one year of follow-up	**46 (13.7%)**	**33 (9.5%)**
95% Confidence Interval*	(-0.6, +9.1%)	
Selected Musculoskeletal Adverse Events in Patients with Arthropathy at One Year of Follow-up**	**Ciprofloxacin N=46 patients*** **	**Comparator N=33 patients*** **
Arthralgia	35	20
Abnormal Joint and/or Gait Exam	11	8
Accidental Injury	6	1
Leg Pain	5	1
Back pain	4	0
Arthrosis	4	1
Bone Pain	3	0
Joint Disorder	2	0
Pain	2	2
Myalgia	1	4
Arm Pain	0	2
Movement Disorder	1	1

*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the comparator group by more than +6.0%. At both evaluations, the 95% confidence interval indicated that it could not be concluded that ciprofloxacin had findings comparable to the comparator.
**events occurring in more than one patient
***a patient with arthropathy may have had more than one event

Arthropathy occurred in all age groups and the rates in the ciprofloxacin arm were consistently higher than in the control arm, as shown in Table 2. The majority of musculoskeletal adverse events (i.e., joints and/or surrounding tissues) were mild or moderate and resolved by the 1 year follow up.

TABLE 2
Rate of Arthropathy at 6 Weeks of Follow-Up in Patients Valid for Safety

Arthropathy	Ciprofloxacin	Comparator
All Patients	31/335 (9.3%)	21/349 (6.0%)
Age Group		
≥ 12 months < 24 months	1/36 (2.8%)	0/41
≥ 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
≥ 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)
≥ 12 years to 17 years	7/32 (21.9%)	6/37 (16.2 %)

The arthropathy rates in patients treated with oral versus those treated with IV (IV alone or sequential IV to oral therapy) at six weeks were different. The arthropathy rates in the oral stratum were 9.1% (27/296) for ciprofloxacin and 6.9% (21/304) for the comparator groups. The arthropathy rates in the IV stratum were 10.3% (4/39) for ciprofloxacin and 0% (0/45) for the comparator groups.

The arthropathy rates were similar between males and females and consistent between treatment groups. The rates were 13.9% (38/273) and 10.6% (30/284) in females compared to 12.9% (8/62) and 4.6% (3/65) in males for ciprofloxacin and comparator, respectively.

Arthropathy rates in patients with cUTI were 12.2% (20/164) for ciprofloxacin versus 9.6% (16/166) for comparator, and in patients with pyelonephritis the rates were 6.4% (11/171) for ciprofloxacin versus 2.7% (5/183) for the comparator.

Arthropathy rates were lower than the overall study rates in Mexico (0% for both ciprofloxacin [0/56] and comparator [0/60], respectively) and Peru (2.3% [2/87] for ciprofloxacin versus 3.4% [3/88] for comparator). There was a bigger difference between treatment group arthropathy rates in the United States (21.0% [13/62] for ciprofloxacin versus 11.3% [8/71] for comparator) than in the overall rates. The arthropathy rate was higher than the overall rate in Caucasians (13.8% [18/130] for ciprofloxacin versus 9.7% [13/134] comparator) and lower than the overall rate in Hispanics (7.8% [8/102] for ciprofloxacin versus 2.8% [3/109] for comparator) and “other” race group (5.3% [5/95] ciprofloxacin versus 3.2% [3/93] comparator).

Neurological Events

The incidence of neurological events from initial dosing through 6 weeks up follow-up was 2.7% (9/335) in the ciprofloxacin group and 2.0% (7/349) in the comparator group. All events were reported in less than 1% of patients in either treatment group, as shown in Table 3.

TABLE 3
Neurological Adverse Events Occurring Through 6 Weeks of Follow-Up
Patients Valid for Safety

Neurological Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	9 (3%)	7 (2%)
Dizziness	3 (<1%)	1 (<1%)
Nervousness	3 (<1%)	1 (<1%)
Insomnia	2 (<1%)	0 (0%)
Somnolence	2 (<1%)	0 (0%)
Abnormal Dreams	0 (0%)	2 (<1%)
Convulsion	0 (0%)	2 (<1%)
Hypertonia	0 (0%)	1 (<1%)
Abnormal Gait	0 (0%)	1 (<1%)

The overall incidence of adverse events at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. The most frequently reported events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of control patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin patients compared to 5.7% (20/349) of the control patients and discontinuation of drug due to adverse events was seen in 3% (10/335) of ciprofloxacin patients and 1.4% (5/349) of control patients.

Adverse events, other than those affecting the musculoskeletal or neurologic systems, that occurred in at least 1% of patients treated with ciprofloxacin by six weeks included: diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8%, and rash 1.8%.

II. Study 100201

Patients were treated for various infections, most commonly otitis media (29% [143/487]) and urinary tract infection (22% [105/487]). They had a variety of underlying diseases, including malignancies, and were receiving multiple concomitant medications.

As in Study 100169, the IPSC evaluated each case for any possible evidence of arthropathy. The incidence rate of arthropathy by six-weeks of follow-up (i.e., Day +42) and at the end of one year of follow-up, as assessed by the IPSC, was 8% (37/487) and 11% (56/487), respectively.

The incidence of arthropathy at 1-year of follow-up was 12.3% (33/269) in females and 10.5% (23/218) in males. As in Study 100169, the arthropathy rate was seen in all age groups.

The incidence of any investigator-reported musculoskeletal adverse event by the 1-year post-treatment follow-up in 487 ciprofloxacin-treated patients was 13% (64 patients). The only musculoskeletal event occurring in > 1% of patients was arthralgia (9.4%; 46 patients). Arthrosis was reported in 3 patients (0.6%) and myalgia in 2 patients (0.4%). Tendon disorder was reported in one patient (0.3%).

The incidence of any neurologic event by 6 weeks of follow-up in ciprofloxacin-treated patients was 7.2 % (28/487). Insomnia (3.5%) was the only event occurring in ≥ 1% of patients.

DSI inspection of selected study sites is pending at the time of this writing.

EFFICACY

I. Study 100169

The Per Protocol population was defined as patients with a diagnosis of cUTI or pyleonephritis, a causative organism(s) at baseline, no inclusion or exclusion criteria or other protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).

The clinical success and bacteriologic eradication rates in the Per Protocol population at 5 to 9 days following the end of therapy (i.e., the Test of Cure visit) were similar between ciprofloxacin and the comparator group as shown in Table 4. The treatment group comparisons for clinical success and bacteriologic eradication were also consistent between Stratum I and II (the oral and IV therapy groups, respectively) for ciprofloxacin and the comparator.

TABLE 4
Clinical Success and Bacteriologic Eradication
at Test of Cure (5 to 9 Days Post-Therapy)

	Ciprofloxacin	Comparator
Randomized Patients	337	352
Per Protocol Patients	211 (63%)	231 (66%)
Clinical Response at 5 to 9 Days Post-Treatment*	95.7% (202/211)	92.6% (214/231)
95% CI [-1.3%, 7.3%]**		
Stratum I (oral)	96.0% (188/196)	93.4% (197/211)
97.5% CI [-2.8%, 8.0%]***		
Stratum II (IV)	93.3% (14/15)	85.0% (17/20)
97.5% CI [-21.7%, 34.5%]***		
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
95% CI [-1.3%, 13.1%]**		
Stratum I (oral)	86.4% (165/191)	80.8% (168/208)
97.5% CI [-2.8%, 14.0%]***		
Stratum II (IV)	86.7% (13/15)	81.3% (13/16)
97.5% CI [-28.5%, 38.5%]***		
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
Escherichia coli	156/178 (88%)	161/179 (90%)

* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.
** Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by strata).
*** Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

II. Study 100201

This was a safety study and therefore did not have any clinical or microbiological efficacy criteria.

CONCLUSIONS AND RECOMMENDATIONS

1. The applicant submitted all the data requested in the Pediatric Written Request. Pediatric exclusivity was granted in December 2003.
2. The data support updating the Cipro® package insert to include safety; and treatment recommendations for pediatric patients between 1 and 17 years of age with complicated urinary tract infection or pyelonephritis.
3. DSI inspections are pending at the time of this writing.

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/s/

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