CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537 / S-049
20-780 / S-013
19-847 / S-027
19-857 / S-031

OFFICE DIRECTOR MEMO

Division Director Review -
Ciprofloxacin for Complicated Urinary Tract Infections and Pyelonephritis in Pediatric Patients

Drug Name Established:	Ciprofloxacin
Proprietary:	Cipro®
Route:	Oral or IV
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
Date of Submissions:	September 23, 2003
PDUFA Goal Date:	March 25, 2004
Applicant:	Bayer Corporation, Pharmaceutical Division 400 Morgan Lane West Haven, Connecticut 06516

Subject: Ciprofloxacin for the treatment of pediatric patients with complicated urinary tract infections (cUTI) and pyelonephritis. These supplemental new drug applications (sNDAs) were submitted in response to the Pediatric Written Request issued May 12, 1999 and amended September 23, 2003

RECOMMENDATIONS:

(1) Approval

These sNDAs should be approved and the labeling should reflect the findings from the studies submitted, and be balanced relative to the information known, as well as the uncertainties regarding the adverse event profile in pediatric patients. In the clinical studies submitted, the incidence of adverse events, including events related to joints and/or surrounding tissues (captured under global terms including arthropathy, arthralgia, pain associated with specific joints) was higher with ciprofloxacin than the non-quinolone comparator drugs. Most events were mild to moderate, the clinical signs and symptoms resolved by the end of the study. On the other hand, it has been published that thousands of children have received ciprofloxacin in clinical studies or in off label use and there have been no reports of debilitating cartilage injury as seen in animals. Nevertheless, because large scale, systematic pediatric data collection has not been undertaken, the possibility that this adverse event could be seen rarely in pediatric patients cannot be ruled out. By way of analogy, ciprofloxacin, as well as other quinolones, has been associated with tendon rupture in adult patients – this event is infrequent and was not recognized with this drug class until years post marketing. Tendon rupture is relevant because (a) it involves ontologically related tissue and (b) was rare and therefore not recognized until post marketing. Of note, while the cartilage damage seen in juvenile dogs and other species is well recognized, the finding of tendon damage in rodents is not generally appreciated (Kashida 1997, Simonin 2000, Shalabaie 2000). Finally, as with all antimicrobials, prudent use of ciprofloxacin is important to minimize development of drug resistance (Cizman)

(2) Labeling for INDICATIONS AND USAGE

(a) The INDICATIONS AND USAGE section of the package insert will be updated to reflec indications approved for adults and indications approved for pediatric patients – currently inhalational anthrax (post-exposure) and the current indication "complicated UTI and pyelonephritis". The labeling will state,

Pediatric patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli*.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS** and **CLINICAL STUDIES**.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

(b) The WARNINGS, PRECAUTIONS, Information to Patients and Pediatric Use subsection, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION and CLINICAL STUDIES sections will also be updated to reflect the efficacy and safety data from these submissions. The CLINICAL PHARMACOLOGY, PRECAUTIONS and ANIMAL PHARMACOLOGY sections will be updated to reflect information from data/studies submitted.

(3) Risk Management/Post Marketing Commitments

In discussions with Bayer, the company has indicated that it does not intend to actively promote the use of ciprofloxacin in pediatric patients, and has agreed to the following risk management plans discussed with the Division, OCTAP/Peds, ODS. These post marketing commitments were submitted to FDA on March 24, 2004.

(a) Voluntarily provide to the Divison any promotional materials (4 weeks in advance) and press releases (1 week in advance) prior to distribution relating to the use of ciprofloxacin for complicated urinary tract infections and/or pyelonephritis in the pediatric population for three years following the approval of these supplemental applications.

(b) Bayer agrees to provide biannual updates on CIPRO usage patterns in the pediatric population with the submission dates being no later than October 31, 2004, April 30, 2005, October 31, 2005, April 30, 2006, October 31, 2006, and April 30, 2007.

(c) Provide expedited (15 day) reporting to the Review Division and the Office of Drug Safety on all serious spontaneous adverse events (including listed events considered serious) in patients 17 years of age of younger until April 30, 2007.

(d) Bayer commits to completing the 5 year observational study (Protocol 100201) for patients receiving ciprofloxacin treatment. Bayer agrees to submit a final research report to the Division by March 2008.

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 (although no pediatric indications were approved at that time). Ciprofloxacin oral and/or IV 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, nosocomial pneumonia, empiric therapy of febrile neutropenia, 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 the Pediatric Exclusivity Written Request (WR) originally issued May 12, 1999, amended October 1, 2001, and finally on 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.
> http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3349t1.pdf

The first pediatric indication approved was post-exposure prevention of inhalational anthrax, because the mortality risk associated with inhalational anthrax was judged to be higher than the risk of adverse reactions, including musculoskeletal adverse reactions, for this infection. This decision was reached by the review team and by the members of the Anti-Infective Advisory Committee (July 2000). Ciprofloxacin was approved for this indication in adults and children in August 2000, thus predating the bioterrorism attack of October 2001.

Ciprofloxacin has been used off label in thousands of children worldwide; Grady reports that health care providers prescribe almost 14,000 courses of fluoroquinolones in children <10 years old, 28,000 in children 10-14 years old and >140,000 in 15-17 year olds (Grady 2003). The Division consulted the Office of Drug Safety for information on quinolone use in pediatric patients (both to learn about current usage of fluoroquinolones, including ciprofloxacin, in pediatric patients, and in preparation for the Anti-Infective Advisory Committee meeting scheduled for May 10, during which the results of gatifloxacin studies in recurrent otitis media and treatment failure of acute otitis media will be discussed) These numbers reported by Grady are similar to numbers provided in our ODS consult. The initial use of ciprofloxacin was in children with cystic fibrosis because of the drug's activity against *Pseudomonas aeruginosa*, and the convenience of oral administration. (Church 1997) Studies of cystic fibrosis patients reported improvement in clinical symptoms (range 87% to 100%), although eradication of *P. aeruginosa* was lower (0% to 69.5%) (Alghasham). Subsequent use expanded to pediatric patients with underlying malignancies, complicated urinary tract infections, gram-negative enteric infections, particularly in parts of the world where resistance to other therapies were seen, suppurative otitis media. (Redmond,Mandell, Cizman, Doherty)

Koyle writes, "Early and effective treatment of UTIs in the pediatric patient is considered essential to prevent long term morbidity and potential mortality from end state renal disease". A limited number of products are approved for use in pediatric patients with complicated urinary tract infections and/or pyelonephritis: ceftazidime, cefixime, TMP/SMX.

The development of antimicrobial resistance is a concern – as with other infections and antimicrobials. *Escherichia coli* resistance to TMP/SMX approaches a third of isolates, ESBLs limit the usefulness of beta lactams, and in some parts of the world, quinolone resistance exceeds 10%.(Gordon, Landain),

Information on toxicity of fluoroquinolones, specifically ciprofloxacin, is presented in the literature. The reported incidence of arthropathy or arthralgia varies, and may differ because of differences in study design, patient population including patient age (relatively low experience in children under 5 years, more experience in children 10-17 years in age) and underlying diseases (cystic fibrosis, urinary tract infections, shigellosis). In some studies, arthopathy is not reported, in others the rates are similar to control agents while some authors reports quinolone rates to be higher than the control, or visa versa. Leibovitz evaluated 201children below the age of 10 randomized to ciprofloxacin 10 mg/kg bid or IM ceftriaxone for invasive diarrhea and reported that joint exams were normal during and after completion of therapy for all patients (Leibovitz). Yee et al evaluated tendon and joint disorders (joint, tendon, cartilage, gait) after use of a fluoroquinolone or azithromycin in patients younger than 19 years and reported 13/1593 (0.82%) with ofloxacin, 37/4531 (0.82%) with ciprofloxacin and 118/15,073 (0.78%) with azithromycin. Chalumeau conducted a multicenter, observational cohort study in pediatric patients ranging from <2 years to puberty who received fluoroquinolones or control drugs and reported musculoskeletal events in 10/276 (3.8%) of the quinolone and 1/249 (0.4%) of the control group that consisted of arthralgias of large joints or myalgias; tendinopathy was not reported. Salam studied 120 children with shigellosis, who were treated with with either ciprofloxacin 10 mg/kg bid x 5days or pivmecillinam (a penicillin) and found joint pain after treatment in 13/71 (18%) ciprofloxacin and 16/72 (22%) control patients - no patient had signs of arthritis. Hampel reported on 1795 children, 1447 (71%) between the ages of 13-17 years, 3% were less than 5 years, who received between 8 mg/kg and 25 mg/kg/day, and in whom 31/2030 treatment courses (1.5%) were associated with arthralgia that was considered mostly mild to moderate in severity and resolved without intervention. Gendrel et al reviewed the literature and report adverse events from 11% to 27% of pediatric patients and articular side-effects in 1% to 9% of pediatric patients; she writes that it is therefore "important to continue the policy of second-line use in children, only after failure of an earlier treatment, and when other antibiotics approved for pediatric use cannot be used."

The effect on growth was evaluated by Bethell in Viet Nam in treating 326 children ages 1-14 years with ciprofloxacin (70 mg/kg over 7 days) or ofloxacin for multidrug resistant typhoid. Growth velocity was compared to age matched controls over a 2 year period. No joint symptoms or joint toxicity was reported and no difference in height and weight at the end of 2 years. Burkhardt et al reviewed published information on skeletal growth for patients up to 12 years after quinolone use and found no effects.

A limited number of reports describe MRI and X-ray findings in patients, including histopathologic findings from 2 CF patients who received up to 9-11 months of ciprofloxacin. (Schaad 1992). These reports do not find articular cartilage damage in these children. During the July 1993 Anti-Infective Advisory Committee, Dr. Schaad described the 2 CF patients who received up to 9-11 months of ciprofloxacin 30 mg/kg/day and in whom MRI exams did not show evidence of athropathogenicity and histologic evaluation of joint post mortem showed normal cartilage. During the meeting, Dr. Schaad further commented on MRI findings in other CF patients who received 3 month courses of ciprofloxacin. The MRI showed "statistically significant increase in articular cartilage thickness...we looked at all the possibilities discussed with the specialists, and our interpretation of this phenomenon is that this observation was due to a transient catch-up growth induced by overall health improvement in these patients." Danisovicova et al evaluated 29 patients with CF by MRI and did not show any difference between ciprofloxacin/ofloxacin treated and non-quinolone treated patients. Burkhardt's review of the literature led to the same conclusion.

This absence of reports in children given the strong signal in juvenile beagle dog studies may well represent a species difference, or may be a signal for a low frequency adverse event that has not been seen or not been reported with the current use of the fluoroquinolones. By way of analogy, tendon rupture, seen

mostly in older patients, was not seen during clinical trials, but was reported during post-marketing and appears to be a relatively infrequent event. (Khaliq)

The fluoroquinolone drugs have been used for decades in adult patients and the class has been associated with adverse reactions involving other body systems. Most adult patients do not report toxicity and the drugs are well-tolerated. [The recognized adverse reactions to fluoroquinolones are reported in the product labeling.] For patients who do report adverse reactions, the most common adverse events involve the gastrointestinal tract and include nausea, vomiting, diarrhea. Central nervous system events have been reported and the ciprofloxacin labeling warns of convulsions, increased intracranial pressure, toxic, psychosis, dizziness, confusion, tremors, hallucinations, depressions and rarely suicidal thoughts or acts; also reported have been nervousness, agitation, insomnia, anxiety, nightmares or paranoia. More recently, peripheral neuropathy and paresthesias have been recognized. Ciprofloxacin with concomintant theophylline use has resulted in serious and fatal reactions. Fatal hypersensitivity reactions have been reported after quinolone use. Phototoxicity may be seen. With some fluoroquinolones, QT prolongation has been demonstrated. Liver toxicity and failure was seen with trovafloxacin and hypo/hyperglycemia has been associated with gatifloxacin. Therefore, it is possible that the serious rare adverse reactions could also be seen in pediatric patients, and therefore, the risk/benefit evaluation of pediatric quinolone use would need to take into considerations not only the potential for joint related events but other adverse reactions shown to be associated with the drug class and with ciprofloxacin specifically.

SUMMARY OF SUBMISSION:

Animal Toxicology Study
(Excerpts from review by Dr. Stephen Hundley, Acting Pharmacology/Toxicology Team Leader)

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 oral dose levels of 10, 30, and 90 mg/kg/day. 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. Recovery and latent arthrotoxicity potential were examined in the recovery groups which were maintained for a period of five dose-free months; a period that covered complete musculoskeletal development. Gross pathology, histopathology, and electron microscopic analysis of chondrocytes evaluated all weight-bearing joints and growth plates (where present) in each dog.

"No evidence (clinical and histopathological) of arthrotoxicity was observed in male and female juvenile dogs dosed for 14 days at the 10 mg/kg/day dose level at the 24-hour post-dosing terminal sacrifice and in male and female dogs held for the 5-month dose-free recovery period. The 30 mg/kg/day dose level did not result in clinical evidence of arthrotoxicity at any time during the study. Half of the juvenile dogs at the terminal sacrifice exhibited gross pathological and/or histopathological evidence of articular cartilage arthrotoxicity. The incidence and severity of the pathological and histopathological observations were reduced but still present in the 5-month post-dose recovery animals. Clinical evidence of arthrotoxicity was observed in 10 of 12 juvenile dogs at the 90 mg/kg/day dose level. These symptoms were resolved by Week 8 (six weeks into the post-dose recovery phase). All juvenile dogs exhibited articular cartilage lesions based upon gross pathology and histopathology at the terminal sacrifice (24 hours following the final dose). Similarly, all animals at the 5-month post-dose recovery sacrifice from the 2-week, 90 mg/kg/day dosing routine exhibited both gross pathological and histopathological evidence of articular cartilage lesions.

"These results indicated that at 30 mg/kg/day, subclinical evidence of arthrotoxicity resulted from 14 days of dosing and that these effects, although diminished, were not completely resolved following a 5-month dose-free recovery period. Plasma area under the concentration vs time curve (AUC) data for ciprofloxacin at the 30 mg/kg/day oral dose level to juvenile dogs (32 $\mu g \cdot hr/ml$) was similar to the range of ciprofloxacin AUC values generated from pediatric patients at the proposed therapeutic dose level (approximately 20 to 40 $\mu g \cdot hr/ml$). The average AUC values resulted in an animal to human dose equivalent ratio of approximately 1.3 (32 $\mu g \cdot hr/ml$ / 24 $\mu g \cdot hr/ml$). The ratio for the 90 mg/kg/day dose level was approximately 3.5 (85 $\mu g \cdot hr/ml$ / 24 $\mu g \cdot hr/ml$) while the 10 mg/kg/day ratio was approximately 0.6 (14 $\mu g \cdot hr/ml$ / 24 $\mu g \cdot hr/ml$).

"The safety issue that appears to be more of a concern for pediatric patients than adult patients is subclinical or clinical arthrotoxicity. Ciprofloxacin plasma AUC levels in juvenile dogs at a dose level that resulted in arthrotoxicity were similar to plasma levels generated in pediatric patients at proposed therapeutic doses of ciprofloxacin."

As noted in all current quinolone labeling and in the currently submitted juvenile dog study, the cartilage injury associated with quinolone use has been recognized and studied and evaluated clinically, by gross pathology, histopathogy, electron microscopy, and biochemically. (Stahlmann 2000) The effect is seen in multiple species, and differences are noted between in terms of incidence in different species and toxicity of different quinolones – whether these reflect actual differences or methodologic differences has not been elucidated, and this remaining uncertainly may be reflected in the cautious approach to the use of these drugs in pediatric patients. The mechanism of injury has not been determined, but working hypotheses include magnesium deficiency by chelating the divalent cation (Echenbacher 2000), inhibition of proteoglycan synthesis, inhibition of mitochondrial dehydrogenase in chondrocytes, (Hildebrand) irregular integrin signaling (Egerbacher 1999, 2001, Simonin, Foster)

The recognition that these products also cause tendon toxicity in animals is less frequently noted. Simonin et al reported on perfloxacin induced Achilles tendon toxicity in rodents given 400 mg/kg body weight characterized by depletion in proteoglycan synthesis followed by synthesis suggesting tissue-specific repair. They proposed that because tendons (as well as cartilage) have low or no perfusion, oxygen pressure is low and the tissue is susceptible to oxidative stress, with formation of superoxide; they were able to block the toxic effect in rodents by addition of N-acetylcysteine. Kashida and Kato reported tendon toxicity in rats that differed among the fluoroquinolones and the doses tested; some could be inhibited by coadministration of dexamethasone and L-NAME, a nitric oxide inhibitor. In their study, ciprofloxacin did not cause tendon injury. Shakibaei et al found ofloxacin caused vacuoles and vesicles in tenocytes of the Achilles tendons with swelling an dilation of cell organelles. The authors note that the "effects observed in tendons show similar pathological features as described earlier in cartilage, indicating that quinolone-induced arthropathy and quinolone-induced tendopathy probably are different clinical manifestations of the same toxic effect on cellular components of connective tissue structures."

The reason these observations are relevant is because tendon damage and rupture have been reported with the fluoroquinolones, including ciprofloxacin. There are differences in that these events have usually been reported in adults, with risk factors including age and steroid use. Nevertheless, these findings are consistent with the signals found in animals. Therefore, the possibility that significant cartilage injury analogous to what has been seen in animals, may be seen in some pediatric patients as more quinolone use is seen in pediatrics should be considered. If such toxicity is seen, it is likely to be rare and to be picked up through spontaneous adverse event reporting.

Population Pharmacokinetic Analysis
See summary by Dr. Dakshina Chilukuri, Clinical Pharmacology/Biopharmaceutics Reviewer.

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.

Appropriate dosing regimens were determined and are reflected in the product labeling in the DOSAGE AND ADMINISTRATION section.

Clinical Trials

Study 100169 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. Finally, efficacy was also evaluated by assessing a patient's clinical and microbiological response to ciprofloxacin or comparator regimen at 5 to 9 days following the end of therapy (i.e., the Test-of-Cure visit).

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 from 10 to 21 days, average 11 days. 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 ± 4 days.

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 within six weeks of treatment in 9.3% (31/335) of ciprofloxacin patients versus 6% (21/349) of comparator patients. All musculoskeletal events occurring by 6 weeks resolved, usually within 30 days of end of treatment.

Radiological studies were to be performed for patients with clinical findings related to possible musculoskeletal adverse events. 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.

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 at six weeks were similar between males and females. 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 at six weeks 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 at six weeks 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).

The cumulative rates of musculoskeletal adverse events by the 1 year follow up were 13.7% (46/335) and 9.5% (33/349), respectively. Arthropathy occurred more frequently in patients treated with ciprofloxacin than control, regardless of whether they received IV or oral drug. By the one year follow up, 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]). 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.

Neurological Events

The incidence of neurological events from initial dosing through 6 weeks 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%.

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.

Study 100201 – Observational study with Safety 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 was expected to resolve within 10 days after the onset of fever ($\geq$ 500 cells per mm^3).

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 written request (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).

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 frequently receiving multiple concomitant medications.

As in Study 100169, an Independent Pediatric Safety Committee (IPSC), including a pediatrician, a pediatric rheumatologist, pediatric orthopedic surgeon, evaluated each case for any possible evidence of arthropathy. The incidence rate of arthropathy by six-weeks of follow-up (i.e., Day +42) in patients treated with ciprofloxacin as assessed by the IPSC was 8% (37/487) and at the end of one year of follow-up the incidence in ciprofloxacin treated patients was 11% (56/487). The rates in the non-quinolone treated patients were lower, consistent with the findings in study 100169.

The incidence of arthropathy at 1-year of follow-up for patients who received ciprofloxacin was 12.3% (33/269) in females and 10.5% (23/218) in males. As in Study 100169, arthropathy was reported 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 ciprofloxacin treated 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 adolescent female patient (0.3%), who was identified as having a fibrocartilagenous tear on MRI, detected 3 weeks after stopping ciprofloxacin treatment because of bilateral wrist pain. The MRI information was not available in the case report form but was found during a Division of Scientific Investigations (DSI) inspection. The patient was an adolescent female who was reported to have bilateral wrist pain and

stopped treatment. The MRI showed a fibrocartilagenous tear in the wrist 4 weeks later and the event was apparently judged to be probably not related because this patient was a gymnast and physical activity may have been the predisposing factor. Nevertheless, the finding should have been reported, tendon ruptures are a rare but recognized adverse reaction attributable to the fluoroquinolone drug class. DSI inspection of the comparative Study 100169 did not disclose similar events. The information on these musculoskeletal events, including the report of fibrocartilagenous tear shall be reflected in the labeling.

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.

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

CONCLUSIONS:

The applicant submitted all the data requested in the Pediatric Written Request. Pediatric exclusivity was granted in December 2003.

The data support updating the Cipro® package insert to include both safety and efficacy results from the comparative clinical trial of compliated urinary tract infections and pyelonephritis, and treatment recommendations for pediatric patients between 1 and 17 years of age.

DSI inspections identified one patient with a fibrocartilagenous tear from Study 100201 that had not been reported in the NDA. Inspection of sites from 100169 did not disclose similar adverse reactions.

An approval letter will be issued. It will contain the post-marketing commitments agreed to by Bayer and listed on page 2 of this document. The letter will advise Bayer that promotion of this indication should include the complete text for the pediatric indication, including the NOTE:, to provide both efficacy and safety information in promotional material.

RECOMMENDATIONS FOR LABELING:

The following information is being added to the ciprofloxacin package inserts for the tablets, suspension and IV preparations.

CLINICAL PHARMACOLOGY:

[redacted]

INDICATIONS AND USAGE: See page 2 of this review
Pediatric patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli.*
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS** and **CLINICAL STUDIES.**) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

3 Page(s) Withheld

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This is the list of references cited in this review (alphabetized), it should not be confused with the REFERENCES section of the package insert.

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