CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-554

Trade Name: Cipro XR Tablets (1 gram)

Generic Name: ciprofloxacin extended-release

Sponsor: Bayer Pharmaceuticals Corporation

Approval Date: August 28, 2003

Indications: Provides for treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-554

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

Dear Mr. Verderame:

Please refer to your new drug application (NDA) dated October 29, 2002, received October 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® XR (ciprofloxacin extended release tablets), 1 gram.

We acknowledge receipt of your submissions dated:

December 13, 2002	March 25, 2003 (2)	June 27, 2003
January 3, 2003	May 2, 2003	July 15, 2003
January 13, 2003	May 9, 2003	July 29, 2003
January 20, 2003	May 30, 2003 (2)	August 5, 2003
January 28, 2003 (2)	June 2, 2003	August 6, 2003
February 14, 2003	June 4, 2003	August 22, 2003
February 20, 2003	June 6, 2003 (2)	August 28, 2003 (2)

This new drug application provides for the use of CIPRO® XR (ciprofloxacin extended release tablets) for complicated urinary tract infections and acute uncomplicated pyelonephritis.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert submitted August 28, 2003) and submitted labeling (immediate container and carton labels submitted October 29, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-554**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated August 28, 2003. These commitments are listed below.

1. Provide confirmative evidence of CIPRO XR efficacy in treating complicated urinary tract infections caused by *P. aeruginosa.*

Protocol Submission:	Within 6 months of the date of this letter
Study Start:	Within 12 months of the date of this letter
Final Report Submission:	Within 39 months of the date of this letter

2. Perform Monte Carlo simulations to obtain steady state estimates of ciprofloxacin systemic exposure after administration of the following regimens. These simulations are to be performed over the ranges of creatinine clearance (CL_{cr}) values specified below for normal renal function and mild, moderate, and severe renal impairment, rather than using a single CL_{cr} value:

   - 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} 50-80 mL/min)
   - 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} 30-50 mL/min)
   - 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)
   - 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} 50-80 mL/min)
   - 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} 30-50 mL/min)
   - 750 mg CIPRO® (immediate release) bid for 14 days in patients with normal renal function (CL_{cr} 81-120 mL/min)

Final Report Submission:	Within 12 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling.

In addition, submit three copies of the introductory promotional materials that you propose to use for this new strength and new indications. Submit all proposed materials in draft or mock-up form, not

final print. Send one copy to this division/ the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to NDA 21-473 and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-473 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling and postmarketing study commitment reports requested above.

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Package Insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht
8/28/03 01:28:48 PM
NDA 21-554

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

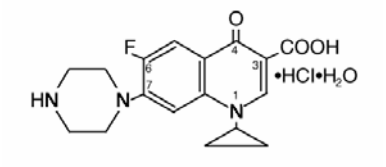
LABELING

CIPRO® XR
(ciprofloxacin* extended-release tablets)

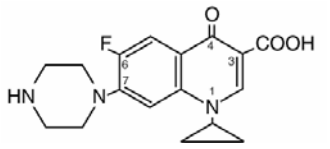
Revised Proposed PI **08/29/03**

DESCRIPTION

CIPRO® XR (ciprofloxacin* extended-release tablets) contains ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO XR Tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride. It is provided as a mixture of the monohydrate and the sesquihydrate. The empirical formula of the mononhydrate is $C_{17}H_{18}FN_3O_3$ • HCl • H_2O and its molecular weight is 385.8. The empirical formula of the sesquihydrate is $C_{17}H_{18}FN_3O_3$ • HCl • 1.5 H_2O and its molecular weight is 394.8. The drug substance is a faintly yellowish to light yellow crystalline substance. The chemical structure of the monohydrate is as follows:



Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. As a hydrate, its empirical formula is $C_{17}H_{18}FN_3O_3$ • 3.5 H_2O and its molecular weight is 394.3. It is a pale yellowish to light yellow crystalline substance and its chemical structure is as follows:



• 3.5 H_2O

CIPRO XR is available in 500 mg and 1000 mg (ciprofloxacin equivalent) tablet strengths. CIPRO XR tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. Each CIPRO XR 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (212.6 mg, calculated on the dried basis). Each CIPRO XR 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin HCl (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (425.2 mg, calculated on the dried basis). The inactive ingredients are crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.

* as ciprofloxacin[†] and ciprofloxacin hydrochloride
[†] does not comply with the loss on drying test and residue on ignition test of the USP monograph.

CLINICAL PHARMACOLOGY

Absorption

CIPRO XR Tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35% of the dose is contained within an immediate-release component, while the remaining 65% is contained in a slow-release matrix.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent.

The following table compares the pharmacokinetic parameters obtained at steady state for these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin immediate-release).

Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO® and CIPRO XR Administration

	C_{max} (mg/L)	AUC_{0-24h} (mg•h/L)	$T_{1/2}$ (hr)	T_{max} (hr)[§]
CIPRO XR 500 mg QD	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0 – 2.5)
CIPRO 250 mg BID	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5 – 2.5)
CIPRO XR 1000 mg QD	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1 – 4)
CIPRO 500 mg BID	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5 – 3.5)

§ median (range)

Results of the pharmacokinetic studies demonstrate that CIPRO XR may be administered with or without food (e.g. high-fat and low-fat meals or under fasted conditions).

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of CIPRO XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine excreted from 12 to 24 hours

after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

Elimination

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations

Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See **PRECAUTIONS, Geriatric Use.)**

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO XR should be reduced to CIPRO XR 500 mg q 24 h in patients with creatinine clearance below 30 mL/min. (See **DOSAGE AND ADMINISTRATION.**)

In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **DOSAGE AND ADMINISTRATION.**)

Drug-drug Interactions

Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc. (See **PRECAUTIONS, Drug Interactions and Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

Antacids: When CIPRO XR given as a single 1000 mg dose (twice the recommended daily dose) was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible. (See **PRECAUTIONS, Information for Patients** and **Drug Interactions**, and **DOSAGE AND ADMINISTRATION**.)

Omeprazole: When CIPRO XR was administered as a single 1000 mg dose concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined. (See **PRECAUTIONS, Drug Interactions**.)

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents

such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $< 10^{-9}$ to $1x10^{-6}$.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus saprophyticus

Aerobic gram-negative microorganisms
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

The following *in vitro* data are available, but their clinical significance is unknown.

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of CIPRO XR in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms
Citrobacter koseri
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized

procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and *Staphylococcus* species:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the following MIC values:

Microorganism		MIC Range (µg/mL)
Enterococcus faecalis	ATCC 29212	0.25 – 2.0
Escherichia coli	ATCC 25922	0.004 – 0.015
Staphylococcus aureus	ATCC 29213	0.12 – 0.5
Pseudomonas aeruginosa	ATCC 27853	0.25 - 1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ciprofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and *Staphylococcus* species:

Zone Diameter (mm)	Interpretation
≥ 21	Susceptible (S)
16 – 20	Intermediate (I)
≤ 15	Resistant (R)

Interpretation should be stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	30 – 40
Staphylococcus aureus	ATCC 25923	22 – 30
Pseudomonas aeruginosa	ATCC 27853	25 - 33

INDICATIONS AND USAGE

CIPRO XR is indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible strains of the designated microorganisms as listed below. CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli, Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus*[a].

Complicated Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*[a].

Acute Uncomplicated Pyelonephritis caused by *Escherichia coli*.

[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO XR may be initiated before results of these tests are

known; once results become available appropriate therapy should be continued. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

CIPRO XR is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPRO XR IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological 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. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity

reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

If a diagnosis of pseudomembranous colitis is established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

PRECAUTIONS

General: Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See **ANIMAL PHARMACOLOGY**.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS, Information for Patients**, and **Drug Interactions.**)

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the

quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

Information for Patients:

Patients should be advised:

- that CIPRO XR may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration with magnesium/aluminum antacids, or sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron, or zinc should be avoided. CIPRO XR may be taken two hours before or six hours after taking these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions**, **DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions.)** CIPRO XR should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, CIPRO XR may be taken with a meal that contains these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions**, **DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.)

- if the patient should forget to take CIPRO XR at the usual time, he/she may take the dose later in the day. Do not take more than one CIPRO XR tablet per day even if a patient misses a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET**.

- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue CIPRO XR at the first sign of a skin rash or other allergic reaction.

- to avoid excessive sunlight or artificial ultraviolet light while receiving CIPRO XR and to discontinue therapy if phototoxicity occurs.

- that if they experience pain, inflammation, or rupture of a tendon to discontinue treatment, to inform their physician, and to rest and refrain from exercise.

- that CIPRO XR may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

- that CIPRO XR may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.

- that convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to notify their physician before taking CIPRO XR if there is a history of this condition.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Absorption of the CIPRO XR tablet was slightly diminished (20%) when given concomitantly with omeprazole. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions.)**

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)
E coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity studies with rats and mice at daily oral dose levels of 250 and 750 mg/kg, respectively (approximately 2 and 3 -fold greater than the 1000 mg daily human dose based upon body surface area).
Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to the maximum recommended daily human dose of 1000 mg based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (1.0 times the highest recommended daily human dose of 1000 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS - the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state there is no risk.

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation. In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures). There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy. However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for the less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.7 and 0.4 times the maximum daily human dose of 1000 mg based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Nursing Mothers: Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made

whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of CIPRO XR in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

Geriatric Use: In a large, prospective, randomized CIPRO XR clinical trial in complicated urinary tract infections, 49% (509/1035) of the patients were 65 and over, while 30% (308/1035) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and clinical experience with other formulations of ciprofloxacin has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTATION.**)

ADVERSE REACTIONS

Clinical trials in patients with urinary tract infections enrolled 961 patients treated with 500 mg or 1000 mg CIPRO XR. Most adverse events reported were described as mild to moderate in severity and required no treatment. The overall incidence, type and distribution of adverse events were similar in patients receiving both 500 mg and 1000 mg of CIPRO XR. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates observed in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In the clinical trial of uncomplicated urinary tract infection, CIPRO XR (500 mg once daily) in 444 patients was compared to ciprofloxacin immediate-release tablets (250 mg twice daily) in 447 patients for 3 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 0.2% (1/444) of patients in the CIPRO XR arm and in 0% (0/447) of patients in the control arm.

In the clinical trial of complicated urinary tract infection and acute uncomplicated pyleonephritis, CIPRO XR (1000 mg once daily) in 517 patients was compared to ciprofloxacin immediate-release tablets (500 mg twice daily) in 518 patients for 7 to 14 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 3.1% (16/517) of patients in the CIPRO XR arm and in 2.3% (12/518) of patients in the control arm. The most common reasons for discontinuation in the CIPRO XR arm were

nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common reason for discontinuation was nausea/vomiting (3 patients).

In these clinical trials, the following events occurred in $\geq$ 2% of all CIPRO XR patients, regardless of drug relationship : nausea (4%), headache (3%), dizziness (2%), diarrhea (2%), vomiting (2%) and vaginal moniliasis (2%).

Adverse events, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of all CIPRO XR treated patients were: nausea (3%), diarrhea (2%), headache (1%), dyspepsia (1%), dizziness (1%), and vaginal moniliasis (1%). Vomiting (1%) occurred in the 1000 mg group.

Additional uncommon events, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of CIPRO XR treated patients were:

BODY AS A WHOLE: abdominal pain, asthenia, malaise, photosensitivity reaction
CARDIOVASCULAR: bradycardia, migraine, syncope
DIGESTIVE: anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst
HEMIC/LYMPHATIC: prothrombin decreased
CENTRAL NERVOUS SYSTEM: abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo
METABOLIC: hyperglycemia
SKIN/APPENDAGES: dry skin, maculopapular rash, pruritus, rash, skin disorder, urticaria, vesiculobullous rash
SPECIAL SENSES: diplopia, taste perversion
UROGENITAL: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide post-marketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications). Because these reactions have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or a causal relationship to drug exposure. The events are:
achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions), anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C difficile* associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, flushing, gastrointestinal bleeding, gout (flare up), gynecomastia, hallucinations, hearing loss, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic necrosis, hiccup, hyperpigmentation, hypertension, hypotension, ileus, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lymphadenopathy, manic

reaction, myalgia, myasthenia gravis (possible exacerbation), myocardial infarction, myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, paranoia, paresthesia, perspiration (increased), phobia, pleural effusion, polyuria, postural hypotension, pseudomembranous colitis, pulmonary embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory distress, restlessness, Stevens-Johnson syndrome, tachycardia, taste loss, tendinitis, tendon rupture, tinnitus, toxic epidermal necrolysis, toxic psychosis, unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing lights, change in color perception, overbrightness of lights).

Laboratory Changes:

The following adverse laboratory changes, in alphabetical order, regardless of incidence or relationship to drug, have been reported in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications):

Decreases in blood glucose, BUN, hematocrit, hemoglobin, leukocyte counts, platelet counts, prothrombin time, serum albumin, serum potassium, total serum protein, uric acid.

Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical lymphocyte counts, blood glucose, blood monocytes, BUN, cholesterol, eosinophil counts, LDH, platelet counts, prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum creatine phosphokinase, serum creatinine, serum gamma-glutamyl transpeptidase (GGT), serum potassium, serum theophylline (in patients receiving theophylline concomitantly), serum triglycerides, uric acid.

Others: albuminuria, change in serum phenytoin, crystalluria, cylindruria, immature WBCs, leukocytosis, methemoglobinemia, pancytopenia.

OVERDOSAGE

In the event of acute excessive overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including administration of magnesium or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent

species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

DOSAGE AND ADMINISTRATION

CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Cipro XR should be administered orally once daily as described in the following Dosage Guidelines table:

DOSAGE GUIDELINES

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500 mg	Q24h	3 Days
Complicated Urinary Tract Infection	1000 mg	Q24h	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg	Q24h	7-14 Days

Patients whose therapy is started with CIPRO I.V. for urinary tract infections may be switched to CIPRO XR when clinically indicated at the discretion of the physician.

CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. A 2-hour window between substantial calcium intake (> 800 mg) and dosing with CIPRO XR is recommended. CIPRO XR should be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET**. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions**, **PRECAUTIONS, Drug Interactions and Information for Patients**.)

Impaired Renal Function:

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. No dosage adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. In patients with complicated urinary tract infections and acute uncomplicated pyelonephritis, who have a creatinine clearance of < 30 mL/min, the dose of CIPRO XR should be reduced from 1000 mg to 500 mg daily. For patients on hemodialysis or peritoneal dialysis, administer CIPRO XR after the dialysis procedure is completed. (See **CLINICAL PHARMACOLOGY, Special Populations, and PRECAUTIONS, Geriatric Use**.)

Impaired Hepatic Function:

No dosage adjustment is required with CIPRO XR in patients with stable chronic cirrhosis. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **CLINICAL PHARMACOLOGY, Special Populations**.)

HOW SUPPLIED

CIPRO XR is available as nearly white to slightly yellowish, film-coated, oblong-shaped tablets containing 500 mg or 1000 mg ciprofloxacin. The 500 mg tablet is coded with the word “BAYER” on one side and “C500 QD” on the reverse side. The 1000 mg tablet is coded with the word “BAYER” on one side and “C1000 QD” on the reverse side.

	Strength	NDC Code
Bottles of 50	500 mg	0026-8889-50
Bottles of 100	500 mg	0026-8889-51
Bottles of 50	1000 mg	0026-8897-50
Bottles of 100	1000 mg	0026-8897-51
Unit Dose Pack of 30	1000 mg	0026-8897-69

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

CLINICAL STUDIES

Uncomplicated Urinary Tract Infections (acute cystitis)

CIPRO XR was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in a randomized, double-blind, controlled clinical trial conducted in the US. This study compared CIPRO XR (500 mg once daily for three days) with ciprofloxacin immediate-release tablets (CIPRO® 250 mg BID for three days). Of the 905 patients enrolled, 452 were randomly assigned to the CIPRO XR treatment group and 453 were randomly assigned to the control group. The primary efficacy variable was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at Test of Cure (Day 4 - 11 Post-therapy).

The bacteriologic eradication and clinical success rates were similar between CIPRO XR and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO XR minus control group are given in the following table:

	CIPRO XR 500 mg QD x 3 Days	CIPRO 250 mg BID x 3 Days
Randomized Patients	452	453
Per Protocol Patients†	199	223
Bacteriologic Eradication at TOC (n/N)*	188/199 (94.5%)	209/223 (93.7%)
CI [-3.5%, 5.1%]		
Bacteriologic Eradication (by organism) at TOC (n/N)**		
E coli	156/160 (97.5%)	176/181 (97.2%)
E faecalis	10/11 (90.9%)	17/21 (81.0%)
P mirabilis	11/12 (91.7%)	7/7 (100%)
S saprophyticus	6/7 (85.7%)	9/9 (100%)
Clinical Response at TOC (n/N)***	189/199 (95.0%)	204/223 (91.5%)
CI [-1.1%, 8.1%]		

* n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/total number of patients

** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

*** n/N = patients with clinical success /total number of patients

† The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria, except for *S saprophyticus* ($\geq 10^4$ CFU/mL).

Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

CIPRO XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients (521 patients per treatment arm) and compared CIPRO XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg BID for 7 to 14 days). The primary efficacy endpoint for this trial was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at 5 to 11 days post-therapy (test-of-cure or TOC) for the Per Protocol and Modified Intent-To-Treat (MITT) populations.

The Per Protocol population was defined as patients with a diagnosis of cUTI or AUP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, no inclusion criteria violation, a valid test-of-cure urine culture within the TOC window, an organism susceptible to study drug, no premature discontinuation or loss to follow-up, and compliance with the dosage regimen (among other criteria). More patients in the CIPRO XR arm than in the control arm were excluded from the Per Protocol population and this should be considered in the interpretation of the study results. Reasons for exclusion with the greatest discrepancy between the two arms were no valid test of cure urine culture, an organism resistant to the study drug, and premature discontinuation due to adverse events.

An analysis of all patients with a causative organism(s) isolated at baseline and who received study medication, defined as the MITT population, included 342 patients in the CIPRO XR arm and 324 patients in the control arm. Patients with missing responses were counted as failures in this analysis. In the MITT analysis of cUTI patients, bacteriologic eradication was 160/271 (59.0%) versus 156/248 (62.9%) in CIPRO XR and control arm, respectively [97.5% CI* (-13.5%, 5.7%)]. Clinical cure was 184/271 (67.9%) for CIPRO XR and 182/248 (73.4%) for control arm, respectively [97.5% CI* (-14.4%, 3.5%)]. Bacterial eradication in the MITT analysis of patients with AUP at TOC was 47/71 (66.2%) and 58/76 (76.3%) for CIPRO XR and control arm, respectively [97.5% CI* (-26.8%, 6.5%)]. Clinical cure at TOC was 50/71 (70.4%) for CIPRO XR and 58/76 (76.3%) for the control arm [97.5% CI* (-22.0%, 10.4%)].

* confidence interval of the difference in rates (CIPRO XR minus control).

In the Per Protocol population, the differences between CIPRO XR and the control arm in bacteriologic eradication rates at the TOC visit were not consistent between AUP and cUTI patients. The bacteriologic eradication rate for cUTI patients was higher in the CIPRO XR arm than in the control arm. For AUP patients, the bacteriologic eradication rate was lower in the CIPRO XR arm than in the control arm. This inconsistency was not observed between the two treatment groups for clinical cure rates. Clinical cure rates were 96.1% (198/206) and 92.1% (211/229) for CIPRO XR and the control arm, respectively.

The bacterial eradication and clinical cure rates by infection type for CIPRO XR and the control arm at the TOC visit and their corresponding 97.5% confidence intervals for the differences between rates (CIPRO XR minus control arm) are given below for the Per Protocol population analysis:

	CIPRO XR 1000 mg QD	**CIPRO 500 mg BID**
Randomized Patients	521	521
Per Protocol Patients^	206	229
cUTI Patients		
Bacteriologic Eradication at TOC (n/N)*	148/166 (89.2%)	144/177 (81.4%)
CI [-0.7%, 16.3%]		
Bacteriologic Eradication (by organism) at TOC (n/N)**		
E coli	91/94 (96.8%)	90/92 (97.8%)
K pneumoniae	20/21 (95.2%)	19/23 (82.6%)
E faecalis	17/17 (100%)	14/21 (66.7%)
P mirabilis	11/12 (91.6%)	10/10 (100%)
P aeruginosa	3/3 (100%)	3/3 (100%)
Clinical Cure at TOC (n/N)***	159/166 (95.8%)	161/177 (91.0%)
CI [-1.1%, 10.8%]		
AUP Patients		
Bacteriologic Eradication at TOC (n/N)*	35/40 (87.5%)	51/52 (98.1%)
CI [-34.8%, 6.2%]		
Bacteriologic Eradication of *E. coli* at TOC (n/N)**	35/36 (97.2%)	41/41 (100%)
Clinical Cure at TOC (n/N)***	39/40 (97.5%)	50/52 (96.2%)
CI [-15.3%, 21.1%]		

^ Patients excluded from the Per Protocol population were primarily those with no causative organism(s) at baseline or no organism present at $\geq 10^5$ CFU/mL at baseline, inclusion criteria violation, no valid test-of-cure urine culture within the TOC window, an organism resistant to study drug, premature discontinuation due to an adverse event, lost to follow-up, or non-compliance with dosage regimen (among other criteria).

* n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/total number of patients

** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

*** n/N = patients with clinical success /total number of patients

Of the 166 cUTI patients treated with CIPRO XR, 148 (89%) had the causative organism(s) eradicated, 8 (5%) had persistence, 5 (3%) patients developed superinfections and 5 (3%) developed new infections. Of the 177 cUTI patients treated in the control arm, 144 (81%) had the causative organism(s) eradicated, 16 (9%) patients had persistence, 3 (2%) developed superinfections and 14 (8%) developed new infections. Of the 40 patients with AUP treated with CIPRO XR, 35 (87.5%) had the causative organism(s) eradicated, 2 (5%) patients had

persistence and 3 (7.5%) developed new infections. Of the 5 CIPRO XR AUP patients without eradication at TOC, 4 were considered clinical cures and did not receive alternative antibiotic therapy. Of the 52 patients with AUP treated in the control arm, 51 (98%) had the causative organism(s) eradicated. One patient (2%) had persistence.

References: 1. NCCLS, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003.
2. NCCLS, Performance Standards for Antimicrobial Disk Susceptibility Tests-Eighth Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

PATIENT INFORMATION ABOUT CIPRO® XR (ciprofloxacin extended-release tablets)

This section contains important patient information about CIPRO XR and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO XR. CIPRO XR can be prescribed only by a licensed health care professional. Your doctor has prescribed CIPRO XR only for you.

CIPRO XR is intended only to treat urinary tract infections and acute uncomplicated pyelonephritis (also known as a kidney infection). It should not be used to treat other infections. Do not give it to other people even if they have a similar condition. Do not use it for a condition for which it was not prescribed. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO XR is right for you.

What is CIPRO XR?

CIPRO XR is an antibiotic in the quinolone class that contains the active ingredient ciprofloxacin. CIPRO XR is specifically formulated to be taken just once daily to kill bacteria causing infection in the urinary tract. CIPRO XR has been shown in clinical trials to be effective in the treatment of urinary tract infections. You should contact your doctor if your condition is not improving while taking CIPRO XR.

CIPRO XR Tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. CIPRO XR is available in ~~a~~ 500 mg and 1000 mg tablet strengths.

How and when should I take CIPRO XR?

CIPRO XR should be taken once a day for three (3) to fourteen (14) days depending on your infection. Take CIPRO XR at approximately the same time each day with food or on an empty stomach. CIPRO XR should not be taken with dairy products (like milk or yogurt) or

calcium-fortified juices alone; however, CIPRO XR may be taken with a meal that contains these products. Should you forget to take it at the usual time, you may take your dose later in the day. Do not take more than one CIPRO XR tablet per day even if you missed a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET**.

You should take CIPRO XR for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection.

Who should not take CIPRO XR?

You should not take CIPRO XR if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones."

CIPRO XR is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO XR, talk to your doctor before taking this medication.

CIPRO XR is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO XR?

CIPRO XR is generally well tolerated. The most common side effects, which are usually mild, include nausea, headache, dyspepsia, dizziness, vaginal yeast infection and diarrhea. If diarrhea persists, call your health care professional. Antibiotics of the quinolone class may also cause vomiting, rash, and abdominal pain/discomfort.

You should be careful about driving or operating machinery until you are sure CIPRO XR is not causing dizziness.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including ciprofloxacin, even after just one dose. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking CIPRO XR and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPRO XR.

Ciprofloxacin has been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPRO XR and call your health care professional.

Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions. Quinolones, including ciprofloxacin, have been

rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

CIPRO XR can affect how other medicines work. Tell your doctor about all other prescriptions and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline or VIDEX® (didanosine) chewable/buffered tablets or pediatric powder. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO XR.

Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO XR and may prevent it from working. You should take CIPRO XR either 2 hours before or 6 hours after taking these products.

Remember:

Do not give CIPRO XR to anyone other than the person for whom it was prescribed.

Complete the course of CIPRO XR even if you are feeling better.

Keep CIPRO XR and all medications out of reach of children.

This information does not take the place of discussions with your doctor or health care professional about your medication or treatment.

Rx Only

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

MEDICAL REVIEW(S)

CLINICAL REVIEW FOR
NEW DRUG APPLICATION # 21-554

Drug: Cipro XR® tablet
(ciprofloxacin HCl and ciprofloxacin extended release)

Applicant's Proposed Indications:

- Complicated urinary tract infection, in men and women, caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis,* [redacted] (b) (4), and *Pseudomonas aeruginosa*[a]*
- Acute uncomplicated pyelonephritis, in men and women, caused by *Escherichia coli*

*On July 29, 2003 the applicant withdrew their proposal to include [redacted] (b) (4) in the indication for complicated urinary tract infection and added a qualifying statement that *P. aeruginosa* was studied in < 10 patients (see below).

[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

General Information:

Applicant Name:	Bayer Corporation, Pharmaceutical Division
Applicant's Address:	400 Morgan Lane West Haven, Connecticut 06516
Applicant's Telephone:	(800) 468-0894

Submission/Review Dates:

Dates of Submission:	October 29, 2002; March 25, 2003; May 2, 2003; May 9, 2003; May 30, 2003; June 2, 2003; June 27, 2003; July 15, 2003; July 29, 2003; August 6, 2003
Date Review Begun:	December 2, 2002
Date Review Completed:	August 20, 2003

Drug Identification:

Generic Name:	ciprofloxacin HCl and ciprofloxacin extended release
Pharmacologic Category:	fluoroquinolone antibiotic
Proposed Trade Name:	Cipro XR®
Molecular Formula:	$C_{17}H_{18}FN_3O_3$ • 3.5 H_2O (ciprofloxacin betaine)
Molecular Weight:	394.3 daltons
Dosage Form:	1000 mg Extended-Release Tablets
Route of Administration:	Oral

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ALT	alanine transaminase
AUC	area under the plasma concentration time curve
AUP	acute uncomplicated pyelonephritis
BID	*bis in die* (twice a day)
C_{max}	maximum plasma concentration
CFU	colony forming units
COSTART	coding symbols for a Thesaurus of adverse reaction terms
cUTI	complicated urinary tract infection
uUTI	uncomplicated urinary tract infection
GGT	gamma glutamyl transpeptidase
[redacted]	(b) (4)
QD	*quaque die* (once daily)
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TOC	test-of-cure
ULN	upper limit of normal
XR	extended release

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

In this submission, the applicant demonstrates the activity of 7 to 14 days of treatment with 1000 mg of ciprofloxacin extended release tablets (Cipro XR) in the treatment of patients with complicated urinary tract infection (cUTI) and acute pyelonephritis (AUP). The efficacy of Cipro XR is compared to a FDA-approved regimen consisting of immediate-release ciprofloxacin 500 mg tablets twice daily (Cipro BID) for 7 to 14 days. The Cipro BID regimen is an acceptable comparator since it is approved for severe/complicated urinary tract infections at a dose of 250 to 500 mg twice daily for 7 to 14 days.

The study enrolled 1,042 patients (521 patients in both the Cipro XR and Cipro BID groups) and the primary endpoint is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in cUTI and AUP patients combined in the valid for efficacy (i.e., Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (–2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

During the review, the Division determined that it was not appropriate to pool results for AUP and cUTI patients due to a significant treatment-by-infection interaction. Therefore, bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer. In addition, the Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. The Division considers analyses of the MITT and PP populations to be co-primary in non-inferiority trials, which is the design of this trial. The MITT population was of particular interest in this trial due to a discrepancy in the number of patients excluded from the PP population between the two treatment arms.

In the MITT population, the bacteriologic eradication rates in AUP patients are 66.2% for Cipro XR compared to 76.3% for Cipro BID [97.5% CI (-26.8, 6.5)]*. In cUTI patients, 59.0% of the Cipro XR group was eradicated compared to 62.9% of the Cipro BID group [97.5% CI (-13.5, 5.7)]*.

In the Per Protocol (PP) population, the bacteriologic eradication rates in AUP patients in are 87.5% for Cipro XR compared to 98.1% for Cipro BID [97.5% CI (-34.8, 6.2)]*. In cUTI patients, 89.2% of the Cipro XR group was eradicated compared to 81.4% of the Cipro BID group [97.5% CI (-0.7, 16.3)]*.

* The calculation of the difference in eradication rates between treatment groups [i.e., (Cipro XR minus Cipro BID)] for each stratum alone (i.e., AUP and cUTI) is adjusted for multiple comparisons.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above –10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

Analyses performed to assess how Cipro XR compared to Cipro BID, with respect to eradication of the baseline pathogen demonstrated comparable eradication rates and clinical response rates.

The applicant demonstrated efficacy of Cipro XR in the PP population of cUTI patients against the following organisms most commonly isolated in urine (≥ 10 in either treatment group): *Escherichia coli* (91/94, 96.8%), *Klebsiella pneumoniae* (20/21, 95.2%), *Enterococcus faecalis* (17/17, 100%), and *Proteus mirabilis* (11/12, 91.6%). For AUP the most common organism was *E. coli* (35/36, 97.2%).

The applicant provided data on less than 10 isolates of *P. aeruginosa* (3/3, 100%), but submitted additional data, including a combination of microbiological data (i.e., MICs) for susceptible isolates of *P. aeruginosa*, along with drug concentration data in plasma and urine, which supports the Division's recommendation of Cipro XR as an appropriate drug to select for the treatment of cUTI caused by susceptible strains of *P. aeruginosa*. The applicant will be asked to continue to gather efficacy and bacteriologic susceptibility information on isolates of *Pseudomonas aeruginosa* in cUTI patients.

The applicant's proposal to reduce the dosage of Cipro XR 1000 mg in patients with severe renal impairment to Cipro XR 500 mg is acceptable. The issue of dosage adjustment of Cipro XR 1000 mg in cUTI and AUP patients with mild to moderate renal impairment has not been addressed by the applicant in this NDA. Upon review of the safety data in the study, the adverse events observed following administration of CIPRO XR 1000 mg to patients with normal renal function and to patients with mild to moderate renal impairment are similar. As a Phase IV commitment, the applicant will be asked to perform Monte-Carlo simulations to characterize drug exposure in patients with mild and moderate renal impairment.

There are no clinically meaningful differences between the Cipro XR and Cipro BID groups in the incidence of any adverse event in the pivotal trial. Of note, however, is the difference in discontinuations due to adverse reactions in the Cipro XR group (5.4%, 28/517) compared to Cipro BID (3.7%, 19/518). The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

In summary, Cipro XR is safe and effective for the treatment of patients with cUTI in patients with susceptible organisms, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* [a], and *Proteus mirabilis*. In addition, Cipro XR is safe and effective for the treatment of patients with AUP in patients with susceptible organisms, including *Escherichia coli*. The recommendation is for approval of Cipro XR 1000 mg once daily for 7 to 14 days for cUTI and AUP.

[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

B. Recommendations on Phase IV Studies and/or Risk Management Steps

- The applicant will be asked to continue to gather efficacy and bacteriologic susceptibility information on isolates of *Pseudomonas aeruginosa* in cUTI patients.
- The applicant will be asked to perform Monte-Carlo simulations to simulate exposure of Cipro XR 1000 mg administered once daily for 14 days to patients with mild and moderate renal impairment (see Clinical Pharmacology and Biopharmaceutics review by Dakshina Chilukuri, Ph.D.).

II. Summary of Clinical Findings

The design for the pivotal study was guided by the following two FDA documents:

- Points to Consider: Urinary Tract Infections. 1997
- Draft Guidance for Industry: Complicated Urinary Tract Infections and Pyelonephritis - Developing Antimicrobial Drugs for Treatment. July 1998.

The applicant also gave consideration to the other following documents when designing this study: the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines (1993), the Committee on Proprietary Medicinal Products' (CPMP) Note for Guidance on Evaluation of New Antibacterial Medicinal Products (1998), and the Infectious Disease Society of America (IDSA) Practice Guidelines Committee publication (1999).

A. Brief Overview of Clinical Program

The primary source of data in support of this application is a prospective, active-controlled, randomized, double blind, multicenter Phase III trial (Study 100275). In this study, a regimen of ciprofloxacin XR 1000 mg once daily tablets administered for 7 to 14 days was compared with the approved (labeled) dosage regimen for conventional (immediate-release) ciprofloxacin tablets (500 mg BID for 7 to 14 days). The protocol inclusion and exclusion criteria for cUTI and AUP are consistent with FDA's 1998 draft guidance document, and included men or non-pregnant women, 18 years of age or older, who presented with clinical signs and symptoms of a cUTI or AUP.

This study was conducted in the United States (US) and Canada at 100 investigative sites. One thousand and forty-two (1,042) adult men and women

with cUTI or AUP were randomized (521 to the Cipro XR group and 521 to the Cipro BID group).

B. Efficacy

Cipro XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients and compared Cipro XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days). The primary endpoint for this trial is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in AUP and cUTI patients combined in the valid for efficacy (Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

There are two problems with the applicant's analysis of bacteriologic eradication in cUTI and AUP patients combined in the Per Protocol (PP) population.

- There is a difference in the treatment effect between patients with AUP and cUTI. The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%). In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the ciprofloxacin BID group (81.4%). The applicant pre-specified in the protocol that a Breslow-Day test for treatment-by-infection interaction would be performed prior to combining data from AUP and cUTI patients. The *P* value for the Breslow-Day test is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients. Therefore, the Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients due to the significant treatment-by-infection interaction.

- The Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. Although not specified in the protocol by the applicant, the Division considers analyses of the MITT and PP populations to be co-primary in non-inferiority trials, which is the design of this trial. When the MITT population is examined along with reasons for exclusion from the PP population, there are significantly more patients in the Cipro XR group (40%, 136/342) than in the Cipro BID group (29%, 95/324) that had been excluded from the PP population. Exclusions from the PP population are primarily a result of premature discontinuations, which are primarily due to adverse events (2.9% versus 1.7%, respectively) and no valid test-of-cure (TOC) urine culture or lost to follow-up (7.7% versus 4.6%, respectively). A differential rate in exclusion may bias the results of any analysis using this population.

Therefore, the bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer and reported for both the MITT and PP populations. Since in the applicant's analysis random assignment of treatment was stratified by infection type, the calculation of the difference in eradication rates between treatment groups for each stratum alone must be adjusted for multiple comparisons (i.e., 97.5% confidence intervals). The bacteriologic eradication rates and their corresponding 97.5% confidence intervals for the differences between rates (Cipro XR minus Cipro BID) for AUP and cUTI patients, at the TOC visit are given in the following table for both the MITT and PP populations.

Bacteriologic Eradication at TOC (+5 to +11 Days) in AUP and cUTI Patients

	MITT*		PP**	
	n/N (% of Patients)	[95% CI of the Difference]	n/N (% of Patients)	[95% CI of the Difference]
AUP Patients				
Cipro XR	47/71 (66.2%)	[-26.8, 6.5]	35/40 (87.5%)	[-34.8, 6.2]
Cipro BID	58/76 (76.3%)		51/52 (98.1%)	
cUTI Patients				
Cipro XR	160/271 (59.0%)	[-13.5, 5.7]	148/166 (89.2%)	[-0.7, 16.3]
Cipro BID	156/248 (62.9%)		144/177 (81.4%)	

* Patients excluded from the Modified Intent-to-Treat group are those with no causative organism at baseline and those who did not receive study drug.

** Patients excluded from the Per Protocol group are those with no causative organism(s) at baseline, no valid TOC urine culture, inclusion/exclusion criteria violation, organism resistant to study drug, protocol violation, non-compliance with dosage regimen, did not receive study drug, inadequate duration of treatment, post-therapy antibiotics, and concomitant antimicrobial therapy.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above –10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

Additional analyses were performed in an attempt to assess how Cipro XR compared to Cipro BID with respect to persistence of the baseline pathogen and subsequent clinical response.

The applicant's definition of the bacteriologic eradication endpoint used in this protocol considers patients with new infections and superinfections to be treatment failures. In the PP population, of the 40 patients with AUP treated with Cipro XR, 35 were eradicated, 2 had persistence (1 *E. coli* and 1 *E. faecalis*), and 3 developed new infections with *E. faecalis* (2 with *E. coli* as baseline pathogen and one with *S. saprophyticus*). Of the 52 patients with AUP treated with Cipro BID, 51 were eradicated. One patient had persistence of *E. faecalis*.

The most common organism isolated from the urine of AUP patients is *E. coli*. The bacteriologic eradication rate for *E. coli* in the PP population is 97.2% (35/36) for the Cipro XR group and 100% (41/41) in the Cipro BID group.

In the PP population, of the 166 patients with cUTI treated with Cipro XR, 148 were eradicated, 8 had persistence, 5 patients developed superinfections, and 5 patients developed new infections. Of the 177 patients with cUTI treated with Cipro BID, 144 were eradicated, 16 had persistence, 3 patients developed superinfections, and 14 fourteen developed new infections.

The most common organisms isolated from the urine of cUTI patients are *E. coli*, *K. pneumoniae*, *E. faecalis*, and *P. mirabilis*. The bacteriologic eradication rates of these organisms in the PP population, in order, are 96.8% (91/94), 95.2% (20/21), 100% (17/17), and 91.6% (11/12) for the Cipro XR group. In the PP population of the Cipro BID group, the rates, in order, are 97.8% (90/92), 82.6% (19/23), 66.7% (14/21), and 100% (10/10).

Results for all the applicant's secondary variables (i.e., bacteriological response at the late follow-up visit and clinical response at the test-of-cure and late follow-up visits), in the PP population for AUP and cUTI patients separately, are summarized as follows:

- The bacteriologic eradication rates at the late follow-up visit in AUP patients are lower in the Cipro XR group (62.5%, 25/40) compared to the Cipro BID group (67.3%, 35/52). In cUTI patients, the rates are higher in the Cipro XR group (59.6%, 99/166) compared to the Cipro BID group (45.2%, 80/177). The differences between the two patient groups follows a similar trend to the results at the TOC visit.

- The clinical response at the TOC visit in AUP patients is similar for the Cipro XR and Cipro BID groups [97.5% (39/40) and 96.2% (50/52), respectively]. In cUTI patients, the response rates are slightly higher in the Cipro XR group (95.8%, 159/166) compared to the Cipro BID group (91.0%, 161/177).

- The clinical response at the late follow-up visit in AUP patients is slightly lower for the Cipro XR group (75%, 30/40) compared to Cipro BID group (80.8%, 42/52). In cUTI patients, the response rates are slightly higher in the Cipro XR group (72.3%, 120/166) compared to the Cipro BID group (61.6%, 109/177).

Differences seen, if any, in bacteriologic eradication rates between younger and older patients, males and females, and those of various races are not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on age, sex, or race.

C. Safety

Of the 1042 patients enrolled in the study, 1035 received at least one dose of study drug and are valid for the analysis of safety (517 in the Cipro XR group and 518 in the Cipro BID group. The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups.

More patients in the Cipro XR group (28 patients or 5.4%) than in the Cipro BID group (19 patients or 3.7%) discontinued study drug due to an adverse event. The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

The most common adverse events in both treatment groups are those occurring in the digestive system [14% (71/517) for Cipro XR and 13% (67/518) for Cipro BID]. The incidence of adverse events for each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30/517) experienced at least one adverse event involving the nervous system compared with 4% (20/518) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [<1%] versus 0 patients [0%], respectively).

Most patients in both treatment groups who experienced adverse events had events that were assessed by the investigator as mild or moderate in intensity. Adverse events that occurred in at least 2% of patients treated with Cipro XR include nausea (5%), headache (3%), diarrhea (3%), vomiting (3%), dizziness (3%), dyspepsia (2%), and vaginal moniliasis (2%). Cipro BID has a similar profile of adverse events occurring in at least 2% of patients, with a slightly higher incidence of headache (5%).

Study drug-related (possible or probable relationship) adverse events were reported in 13% (68/517) of patients in the Cipro XR group and 14% (70/518) of patients in the Cipro BID group. Those occurring in 2% or more of patients in either treatment group include headache, nausea, diarrhea, dizziness, and vaginal moniliasis.

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event assessed by the investigator as severe in intensity. The number of severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Four patient deaths were reported during the study (3 in the Cipro XR group and one in the Cipro BID group). All four patients were in the older age range (76 to 95 years), had a diagnosis of cUTI with one underlying condition, and had other

concurrent medical conditions requiring concomitant medications. In all cases, the adverse event resulting in death was judged by the investigator to be of unlikely or no relationship to study drug. This Reviewer concurs with the investigator's opinion in all cases.

Patients experiencing non-fatal serious adverse events (SAEs) is 5% in both treatment groups, (28/517 and 24/518, respectively). All SAEs reported in the Cipro XR group were judged by the investigators to be unlikely or not related to study drug.

In the two treatment groups, the incidence of clinically significant (>1.8 x ULN) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that are >3 x ULN, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients (<1%) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. In both cases, the events resolved and did not require discontinuation of study drug. Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline.

The incidence of other laboratory test abnormalities is low and comparable between the two treatment groups. Descriptive statistics of the change from baseline in laboratory test results does not reveal any trends that appear to be uniquely associated with Cipro XR treatment.

Overall, there are no clinically meaningful differences in the safety profile of either treatment on the basis of age, sex, or race.

D. Dosing, Regimen, and Administration

The dosage regimen of Cipro XR 1000 mg administered daily for 7 to 14 days for the treatment of cUTI and AUP is based on Phase I studies of this formulation and the approved labeling for conventional ciprofloxacin tablets. The current recommended dosage for ciprofloxacin tablets in the treatment of mild/moderate to severe/complicated urinary tract infections is 250 to 500 mg BID for 7 to 14 days. The Phase I studies for Cipro XR (Studies 10324 and 10339) indicate that the ciprofloxacin AUC attained following the oral administration of Cipro XR 1000 mg tablets every 24 hours is similar to the values attained following the oral administration of conventional ciprofloxacin 500 mg tablets every 12 hours (16.5 mg*h/L versus 16.0 mg*h/L, respectively, in Study 10324; and 15.4 mgh/L versus 14.8 mg*h/L, respectively, in Study 10339). The C_{max} of Cipro XR 1000 mg given every 24 hours is about 46% higher than the C_{max} for Cipro 500 mg tablets given every 12 hours.

E. Special Populations

Pediatric patients (< 18 years) and patients with significant renal impairment (serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/min*1.73 m^2) or hepatic impairment (baseline SGOT or SGPT and/or total bilirubin greater than 3 times the upper limit of normal), and pregnant women were excluded from the Cipro XR development program. Therefore it is not possible to comment on the efficacy or adverse event profile in these populations.

1. Efficacy

Age

In the Reviewer's opinion, differences, if any, seen in the bacteriologic eradication rates between the following patient groups are not considered clinically meaningful: young (< 65 years) and old (≥ 65 years); male and female; Caucasians, Blacks, and Hispanics. No adjustments to the dosing of Cipro XR are warranted based on age, sex or race.

2. Safety

Age

In the Reviewer's opinion, differences, if any, seen in adverse events reported for the following patient groups are not considered clinically meaningful: young (< 65 years) and old (≥ 65 years); male and female; Caucasians, Blacks, and Hispanics. Reporting of adverse events by age, sex, or race are not warranted in the labeling of Cipro XR.

CLINICAL REVIEW

I. Introduction and Background

A new extended-release formulation of ciprofloxacin tablets (Cipro XR) has been developed in 500 mg and 1000 mg (ciprofloxacin equivalent) strengths and is intended to be dosed once daily. The Cipro XR 500 mg tablet was approved for the treatment of patients with uncomplicated urinary tract infections (uUTI) on December 13, 2002. The Cipro XR 1000 mg tablet is intended for the treatment of patients with complicated UTI (cUTI), including acute uncomplicated pyelonephritis (AUP) and is the subject of this NDA submission.

Prior to the approval of Cipro XR for uUTI, there were two other marketed oral formulations of ciprofloxacin: Cipro® tablets (ciprofloxacin hydrochloride) and Cipro® oral suspension (ciprofloxacin). Both formulations are approved for the treatment of the following infections caused by susceptible strains of specifically identified microorganisms: acute sinusitis, lower respiratory tract infections, urinary tract infections, chronic bacterial prostatitis, skin and skin structure infections, bone and joint infections, infectious diarrhea that warrants antibacterial therapy, typhoid fever, nosocomial pneumonia, acute uncomplicated cystitis in females, empiric therapy of febrile neutropenic patients, complicated intraabdominal infections, uncomplicated cervical and urethral gonorrhea, and post-exposure inhalation anthrax. The maximum oral daily dose of Cipro® tablets and oral suspension approved for use in humans is 750 mg twice daily.

Cipro XR is formulated to release drug at a slower rate compared to the conventional immediate release tablets. Approximately 35% of the dose XR dose of ciprofloxacin is contained within an immediate release component, while the remaining 65% is contained in a slow release matrix. Cipro XR is designed to release the entire dose prior to the tablet reaching the distal region of the small intestine.

The Cipro XR formulation exhibits dissolution characteristics aimed to deliver the equivalent exposure to drug, in terms of area under the curve (AUC) as the corresponding approved conventional ciprofloxacin tablet BID treatment. In other words, one Cipro XR 1000 mg tablet has a similar AUC compared with two 500 mg conventional ciprofloxacin tablets given at once. Although the AUC of the two formulations is similar, the peak concentration (C_{max}) achieved with Cipro XR is lower compared to an equivalent dose of the conventional tablet. In other words, one Cipro XR 1000 mg tablet has a lower C_{max} than two 500 mg conventional ciprofloxacin tablets given at once.

A. Established and Proposed Trade Name of Drug, Drug Class, Applicant's Proposed Indications, Dose, Regimens, Age Groups

Drug

Generic Name:	ciprofloxacin HCl and ciprofloxacin extended release
Pharmacologic Category:	fluoroquinolone antibiotic
Proposed Trade Name:	Cipro XR®
Molecular Formula:	$C_{17}H_{18}FN_3O_3$ • 3.5 H_2O (ciprofloxacin betaine)
Molecular Weight:	394.3 daltons
Dosage Form:	1000 mg Extended-Release Tablets
Route of Administration:	Oral

Applicant's Proposed Indications:

- Complicated urinary tract infection, in men and women, caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis,* (b) (4) *, and Pseudomonas aeruginosa*[a]*
- Acute uncomplicated pyelonephritis, in men and women, caused by *Escherichia coli*

*On July 29, 2003 the applicant withdrew their proposal to include (b) (4) in the indication for complicated urinary tract infection and added a qualifying statement that *P. aeruginosa* was studied in < 10 patients (see below).

[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

Applicant's Proposed Dosing and Administration

Indication	Unit Dose	Usual Duration
Complicated Urinary Tract Infection	1000 mg	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg	7-14 Days

B. State of Armamentarium for Indications

1. Other FDA-approved Quinolones

Ciprofloxacin (Cipro®): Urinary Tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloace, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Ofloxacin (Floxin®): Complicated UTI due to *Citrobacter diversus*, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae*, or *Pseudomonas aeruginosa** (*denotes efficacy in less then 10 cases).

Levofloxacin (Levaquin®): Complicated UTI (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloace, Proteus mirabilis, Pseudomonas aeruginosa,* or *Enterococcus faecalis.* Acute pyelonephritis (mild to moderate) caused by *Escherichia coli*.

Lomefloxacin (Maxaquin®): Complicated UTI due to *Citrobacter diversus*, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, or *Enterobacter cloace**(*denotes efficacy in less then 10 cases).

NOTE: In clinical trials in patients experiencing CUTIs due to *Pseudomonas aeruginosa*, 12 of 16 patients had the microorganism eradicated from the urine after therapy with lomefloxacin. None of the patients had concomitant bacteremia. Serum levels of lomefloxacin do not reliably exceed the MIC of Pseudomonas isolates. THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN TREATING PATIENTS WITH PSEUDOMONAS BACTEREMIA HAVE NOT BEEN ESTABLISHED.

Enoxacin (Penetrex®): Complicated UTI due to *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae*, *Enterobacter* cloace, *Staphylococcus epidermidis,* and *Pseudomonas aeruginosa*. (*Efficacy for this organism was studied in fewer than 10 infections.)

Gatifloxacin (Tequin®): Complicated UTI due to *Escherichia coli, Proteus mirabilis,* or *Klebsiella pneumoniae*. Pyelonephritis caused by *Escherichia coli.*

2. Quinolone that did not receive approval for the cUTI and AUP Indication

Trovafloxacin (Trovan®): Based on a randomized, comparative, double-blind trial of trovafloxacin and ciprofloxacin in the treatment of complicated urinary tract infections and a supportive non-comparative study, the MO did not recommend approval for the requested indication of complicated UTI caused by *Escherichia coli* and *Klebsiella pneumoniae.* This decision was based on the inability of the applicant to show equivalence with an approved comparator. Additionally, the MO found that the overall bacteriologic efficacy rate at the EOT (cumulative: 152/196 (77.5%) was lower that that of other approved quinolone antimicrobials. Cumulative pathogen eradication rates for the requested pathogens, *Escherichia coli* and *Klebsiella pneumoniae* were also lower.

3. Other FDA-approved Antibacterials (other than quinolones)

Trimethoprim/Sulfamethoxazole (Bactrim®): for the treatment of UTIs due to susceptible strains of the following organisms: *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae*, *Enterobacter* spp., *Morganella morganii,* and *Proteus vulgaris*.

Sulfisoxazole (Gantrisin®): Acute, recurrent, or chronic UTIs (primarily pyelonephritis, pyelitis, and cystitis,) due to susceptible organisms (usually *Escherichia coli, Klebsiella- Enterobacter, Staphylococcus, Proteus mirabilis* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies.

Loracarbef (Lorabid®): Uncomplicated pyelonephritis caused by *Escherichia coli.*

Cefepime (Maxipime®): Uncomplicated and Complicated UTIs (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae when the infection is severe, or caused by Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis,* when the infection is mild to moderate, including cases associated with concurrent bacteremia associated with these microorganisms.

4. Efficacy of Conventional Ciprofloxacin versus Comparators for cUTI and AUP

Ciprofloxacin has been marketed worldwide since 1988 and is approved to treat mild/moderate to severe/complicated UTI. The recommended dosage regimen for conventional ciprofloxacin tablets or oral suspension is 250 to 500 mg BID for 7 to 14 days.

The efficacy of ciprofloxacin in treating cUTI and AUP infections compared to other antimicrobials can be seen in Tables 1 and 2, respectively.

TABLE 1
Prospective, Randomized, Double Blind, Controlled Clinical Studies Evaluating Treatment of Conventional Ciprofloxacin In Complicated Urinary Tract Infections

Treatment (dose and duration)	Bacteriologic Cure[a] (end of treatment)	Clinical Cure[a] (end of treatment)	Follow-up Efficacy	Reference
Ciprofloxacin 250 mg BID x 7 days	136/151 (90%)[b,c]	140/144 (77%)[b]	111/114 (77%)[d,e]	1
Ofloxacin 200 mg BID x 7 days	130/149 (87%)	108/142 (76%)	108/142 (76%)	
Ciprofloxacin 500 mg BID x 10-14 days	194/240 (81%)[f]	198/231 (86%)[f]	186/219 (84%)[g]	2
Sparfloxacin 200 mg x 1 day followed by 100 mg once daily x 9 to13 days	168/233 (72%)	193/221 (87%)	181/215 (84%)	
Ciprofloxacin 500 mg BID x 10 days	93%[b,j]	100/113 (89%)[b]	Relapse:[i] 10	3
Levofloxacin 250 mg QD x 10 days	91%	116/126 (92%)	Relapse: 13	
Ciprofloxacin 500 mg BID x 7-10 days	62/83 (83%)[b,h]	70/75 (93%)[b]	52/70 (74%)[j]	4
Gatifloxacin 400 mg QD x 7-10 days	61/66 (92%)	61/66 (92%)	51/61 (84%)	

a Evaluable patients
b 5 to 9 days post-treatment
c Urine culture sterile
d 28 to 42 days post-treatment
e Urine culture sterile and clinical cure symptom-free at follow-up visits
f 4 to 14 days post-treatment
g Continued clinical cure at 15 to 56 days post-treatment
h Eradication
i 4 to 6 weeks post-treatment
j Clinical cure at 29 to 42 days post-treatment

References for Table 1

1. Raz R, Naber KG, Raizenberg C, et al. Ciprofloxacin 250 mg twice daily versus ofloxacin 200 mg twice daily in the treatment of complicated urinary tract infections in women. Eur J Clin Micro Infect Dis 2000;19:327-31.

2. Naber KG, di Silverio F, Geddes A, al. e. Comparative efficacy of sparfloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection. J Antimicrob Chemother 1996 May;37 Suppl A:135-44.

3. Richard GA, Childs SJ, Fowler CL, et al. Safety and efficacy of levofloxacin versus ciprofloxacin in complicated tract infections in adults. Pharmacy and Therapeutics 1998 (October);23:534-42.

4. Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind, multi-center comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infections and pyelonephritis. Clin Therapeutics 2002;24:223-36.

TABLE 2
Prospective, Randomized, Double Blind, Controlled Clinical Studies Evaluating Treatment of Conventional Ciprofloxacin In Acute Uncomplicated Pyelonephritis

Treatment (dose and duration)	Bacteriologic Cure[a] (end of treatment)	Clinical Cure[a] (end of treatment)	Follow-up efficacy	Reference
Ciprofloxacin 500 mg BID x 7 days ± initial 400 mg IV dose	112/113 (99%)[b,d]	109/113 (96%)[b,c]	96/106 (91%)[e,f]	1
Trimethoprim/ Sulfamethoxazole 160/800 mg BID x 14 days ± initial 1 gram IV ceftriaxone	90/101 (89%)	92/111 (83%)	82/106 (77%)	
Ciprofloxacin 500 mg BID	94%[g,i]	51/58 (88%)[g]	≤6.5%[h]	2
Levofloxacin 250 mg QD	95%	82/89 (92%)	13%	
Lomefloxacin 400 mg QD	94%	31/39 (80%)	≤6.5%	
Ciprofloxacin 500 mg BID x 7-10 days	17/20 (85%)[g,i] *E. coli* 100%	19/20 (95%)[g]	18/19 (95%)[i]	3
Gatifloxacin 400 mg QD x 7-10 days	23/25 (92%) *E. coli* 95%	25/25 (100%)	22/25 (88%)	

a Evaluable patients
b 4 to 11 days post-treatment
c 95% CI, 0.06 - 0.22 for the difference, P=0.002
d 95% CI, 0.04 – 0.16 for the difference, P=0.004
e Continued clinical cure 22 to 48 days post-treatment
f 95% CI, 0.03 – 0.23 for the difference, P=0.02
g 5 to 9 post days treatment
h Microbiologic relapse rate at 4 to 6 weeks
i Clinical cure at 29 to 42 days post-treatment

References for Table 2

1. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. JAMA 2000;283(12):1583-90.

2. Richard GA, Klimberg IN, Fowler CL, et al. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. Urology 1998;52:51-5.

3. Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind, multi-center comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infections and pyelonephritis. Clin Therapeutics 2002;24:223-36.

C. Important Milestones in Product Development

The regulatory history of Cipro XR 1000 mg tablets for the treatment of cUTI and AUP is outlined in the following sequence of events:

On November 29, 2000, Bayer submitted the IND (61,331) for Cipro® XR* (Ciprofloxacin) extended-release tablets.

On February 13, 2001, a pre-IND/End of Phase II meeting was held with the FDA. The FDA agreed one trial in patients with complicated urinary tract infections would be acceptable for registration. The Division recommended a 10% delta. After the meeting, Bayer proposed that separate NDAs be submitted for uncomplicated and complicated urinary tract infection and the FDA agreed.

Cipro XR* for uncomplicated urinary tract infection (NDA 21-473) was submitted on March 4, 2002.

Cipro XR for uncomplicated urinary tract infection (NDA 21-473) was approved on December 13, 2002. The indication reads as follows:

> **Uncomplicated Urinary Tract Infections (Acute Cystitis)** caused by *Escherichia coli, Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus*[a].

[a] Treatment of infections due to this organism in this organ system was studied in fewer than 10 patients.

* The original trade name proposed by Bayer was (b) (4). On June 6, 2002 at a meeting with the Division as well as representatives from Office of Drug Safety and DDMAC, the (b) (4) portion of the drug name was discussed. It was suggested by the Agency that another suffix similar to other approved extended release products would be more appropriate. On July 18, 2002, Bayer submitted a letter confirming the change in trade name from Ciprofloxacin (b) (4) to Cipro XR (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets).

D. Other Relevant Information

The United States is the first country in which Bayer has submitted an application for approval of ciprofloxacin XR 1000 mg oral tablets. However, multiple submissions around the world in the months following this submission are planned.

Immediate release ciprofloxacin has been studied previously under multiple IND and NDAs.

Product	Form	IND Reference #	NDA Reference #
Oral Tablet	Ciprofloxacin HCl	21,804	19-537
Intravenous	Ciprofloxacin	25,173	19-847
Intravenous 0.2% in 5% Dextrose	Ciprofloxacin	25,173	19-857
Intravenous 0.2% in 0.9% Saline	Ciprofloxacin	25,173	19-858
Oral Suspension	Ciprofloxacin	43,007	20-780

II. Significant Findings from Chemistry, Pharmacology/Toxicology, Microbiology, Clinical Pharmacology/Biopharmaceutics, and Biostatistics

A. Chemistry

This application can be approved from the chemistry perspective.

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Cipro XR 1000 mg. During the review a number of issues, including the following were resolved:

- The acceptance criteria, included in the specification for one of the drug substances (i.e., ciprofloxacin base), were revised.

- The specification for the drug product was also revised to include test and acceptance criteria for water content. Acceptance criteria for the impurities in the drug product were revised.

The trade name was found accepatble by OPDRA and by the Division (HFD-590) for this NDA. The established name was further consulted with the Labeling and Nomenclature Committee and they recommended the following:

> CIPRO XR (ciprofloxacin* extended-release tablets)
> * as ciprofloxaxin † and ciprofloxacin hydrochloride
> † does not comply with the loss on drying test and residue on ignition test of the USP monograph.

See complete review by Dorota Matecka, Ph.D., Chemistry Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-554).

B. Pharmacology/Toxicology

This application can be approved from the pharmacology/toxicology perspective.

The applicant did not submit new pharmacology/toxicology data in support of this NDA only a cross-reference statement to the previously approved Cipro IV, Cipro tablets, and Cipro oral suspension NDAs, as agreed upon with the Division.

See review by Steven Hundley, Ph.D., Pharmacology/Toxicology Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-554).

C. Microbiology

This application can be approved from the microbiological perspective.

See complete review by Peter A. Dionne, M.S., Microbiologist in HFD-590 (DSPIDP) filed with this NDA (21-554).

During the clinical study (100275) the susceptibility of the causative organisms was determined at the central laboratory (b) (4). Broth microdilution susceptibility tests were performed according to National

Committee for Clinical Laboratory Standards (NCCLS) guidelines. *Escherichia coli* was the most frequently isolated organism (n=263), followed by *Klebsiella pneumoniae* (n=50), *Enterococcus faecalis* (n=46), and *Proteus mirabilis* (n=26). The MIC_{90} for *E. coli* was 0.06 µg/mL, while the MIC_{90} for *K. pneumoniae* and *P. mirabilis* were 0.5 µg/mL and 2 µg/mL, respectively. The MIC_{90} for the other 46 isolates of Enterobacteriaceae was ≤ 1 µg/mL and the MIC_{90} for *E. faecalis* was 2 µg/mL.

The by-pathogen eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. Eradication rates for *E. coli*, by far the most common organism, were high for both treatment groups. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginos*a. Persistence was not associated with elevated MICs for any of the organisms.

In patients valid for efficacy that had bacteriologic persistence or were clinical failures at the TOC and follow-up visits, there were more bacteriologic persistence and clinical failures seen in the Cipro BID group (n = 26) compared with the Cipro XR group (n = 15).

The development of resistance during therapy was low.

D. Clinical Pharmacology/Biopharmaceutics

See complete review by Dakshina Chilukuri, PhD, Clinical Pharmacology/Biopharmaceutics Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-554).

A total of five clinical pharmacology studies were conducted with Cipro XR 1000 mg in healthy volunteers. These studies compared pharmacokinetics of the Cipro XR 1000 mg once-daily regimen to the corresponding immediate release regimen (e.g., 1000 mg XR vs. 500 mg immediate release BID) and examined the effects of food on the performance of the XR tablet. In addition, the drug interaction studies to study the effect of Maalox and Omeprazole on the pharmacokinetics of Cipro XR were also conducted. These studies were reviewed in NDA 21-473 as part of the Cipro XR 500 mg tablet formulation.

The 24-hour area under the curve (AUC) obtained following administration of 1000 mg Cipro XR was shown to be equivalent to that attained with BID dosing of 500 mg immediate release ciprofloxacin. The bioavailability of the XR tablet was not altered by administration with food (either a high-fat or a low-fat meal), and did not change upon multiple dosing for 5 days. The C_{max} following administration of the 1000 mg XR tablet was higher than that observed for the 500 mg immediate release tablet. Trough plasma concentrations are lower with the 1000 mg XR once-daily regimen compared to the 500 mg BID regimen. However, urine concentrations of ciprofloxacin following dosing with 1000 mg Cipro XR are maintained well above (>100-fold) the *in vitro* MIC_{90} for *Escherichia coli* (about 0.03 µg/mL).

The applicant's proposal to reduce the dosage of Cipro XR 1000 mg in patients with severe renal impairment to Cipro XR 500 mg is acceptable. The issue of

dosage adjustment of Cipro XR 1000 mg in cUTI and AUP patients with mild to moderate renal impairment has not been addressed by the applicant in this NDA. Specifically, it is unknown if the C_{max} and AUC following administration of Cipro XR 1000 mg to patients with mild to moderate renal impairment would result in exposure causing higher incidence of adverse events.

Upon review of the safety data in Clinical Study 100275 [see more details in this review], the adverse events observed following administration of CIPRO XR 1000 mg to patients with normal renal function and to patients with mild to moderate renal impairment are similar. However, the exposure following administration of Cipro XR 1000 mg in patients with mild to moderate renal impairment is likely to be higher than the exposure obtained after administration of 750 mg bid of immediate relase ciprofloxacin (the highest approved dose). But considering the overall safety profile of Cipro XR in this NDA, it may be acceptable to administer a dose of Cipro XR 1000 mg to patients with mild to moderate renal impairment suffering from cUTI and AUP.

In summary, this application can be approved from the clinical pharmacology and biopharmaceutics perspective. For patients with mild and moderate renal impairment, no dosage adjustments are recommended, at this time. As a Phase IV commitment, the applicant will be asked to perform additional Monte-Carlo simulations to characterize the exposure of Cipro XR 1000 mg (administered once daily for 14 days) in patients with mild and moderate renal impairment. Based on these results, changes in labeling may be recommended at a later time.

E. Biostatistics

The results of the treatment group comparisons of the primary efficacy endpoint (i.e., bacteriologic outcome at TOC) between infection types were not consistent in the clinical study (100275). A treatment-by-infection-type interaction was observed indicating that the treatment effect is different between AUP patients and cUTI patients and as such these two strata should be considered separately.

Within the cUTI stratum, it is the opinion of the statistical reviewer that Cipro XR has been shown to be noninferior to Cipro XR for the bacteriological eradication rate at TOC endpoint in the PP analysis group. Analysis of the mITT group for this endpoint included disproportionately more subjects in the Cipro XR arm who were excluded from the PP analysis group. The majority of these subjects were considered failures in the analysis since their bacteriological response at TOC was likely missing or indeterminate. Within the cUTI stratum in the mITT group, the noninferiority criterion was not met.

Within the AUP stratum, it is the opinion of the statistical reviewer that noninferiority of Cipro XR to Cipro BID for the bacteriological eradication rate at TOC endpoint in the PP analysis group has not been demonstrated. In fact within the AUP stratum, Cipro XR appears to be worse than Cipro BID for the eradication at TOC endpoint in the PP analysis group. A similar trend is observed in the mITT group for this endpoint.

These results for the primary endpoint within each of the strata are not dependent on the use of the expanded 5 to11 day TOC window rather than the 5 to 9 day window defined in the original protocol.

Secondary endpoints for this study included the bacteriological response at follow-up and clinical responses at TOC and follow-up.

- The eradication rates at follow-up for the cUTI subjects were higher in the Cipro XR group than in the Cipro BID group. Conversly, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro BID group than in the Cipro XR group. These trends are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata.

- The clinical success rates at TOC for the cUTI subjects in the PP analysis group were slightly higher in the Cipro XR group than in the Cipro BID group. The clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro BID and Cipro XR groups in the PP analysis group. The Cipro XR group had slightly lower clinical success rates than the Cipro BID group in the mITT analysis.

- The success rates at the follow-up visit for the cUTI subjects in the PP analysis group were higher in the Cipro XR group than in the Cipro BID group. Conversely, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR group than in the Cipro BID group in the PP analysis group. Similar trends were observed in the mITT analysis. These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint.

It is the opinion of the statistical reviewer that Cipro XR has been shown to be non-inferior to Cipro BID in terms of the bacteriologic endpoint at TOC in cUTI subjects. Noninferiority of Cipro XR in comparison to Cipro BID in terms of the bacteriologic endpoint at TOC within AUP subjects has not been demonstrated.

See complete review by Ruthanna Davi, M.S., Biostatistican in HFD-590 (DSPIDP) filed with this NDA (21-554).

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Ciprofloxacin XR tablets 1000 mg are bi-layer tablets composed of an immediate release layer, a controlled release layer, and a coating.

The outer controlled release layer releases approximately 35% of the dose immediately after intake, and the inner immeidate release layer has an immediate onset of release with a marginally slower release rate profile. Both the immediate-release and controlled-release layers of the tablets are composed of different ratios of ciprofloxacin hydrochloride and ciprofloxacin base.

The XR formulation was designed to deliver the equivalent drug exposure (in terms of AUC) as the approved conventional ciprofloxacin daily dose (i.e., 1000 mg Cipro XR is equivalent to two 500 mg conventional ciprofloxacin tablets). Although the two formulations have similar AUCs, the peak concentration (C_{max}) achieved following a 1000 mg dose of the XR formulation is higher than that achieved with the 500 mg dose of the conventional ciprofloxacin tablet.

Through all phases of development the same formulation has been used.

Reviewer's Comment: The following information on the pharmacokinetics of Ciprofloxacin XR 500 mg and 1000 mg is from the applicant's proposed label (May 30, 2003). The data has been verified by the Clinical/Pharmacology Reivewer.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent.

The following table compares the pharmacokinetic parameters obtained at steady state for these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin immediate-release).

Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO® and CIPRO XR Administration

	C_{max} (mg/L)	$AUC_{0\text{-}24h}$ (mg•h/L)	$T_{1/2}$ (hr)	T_{max} (hr)§
CIPRO XR 500 mg QD	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0 – 2.5)
CIPRO 250 mg BID	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5 – 2.5)
CIPRO XR 1000 mg QD	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1 – 4)
CIPRO 500 mg BID	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5 – 3.5)

§ median (range)

Results of the pharmacokinetic studies demonstrate that CIPRO XR may be administered with or without food (e.g. high-fat and low-fat meals or under fasted conditions).

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of CIPRO XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine

excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

Metabolism
Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

Elimination
The elimination kinetics of ciprofloxacin are similar for the immediate-release and the CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations
Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant.

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. For indications where 1000 mg is the appropriate dose, the dosage of CIPRO XR should be reduced to CIPRO XR 500 mg q 24 h in patients with creatinine clearance below 30 mL/min.

In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of

ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Drug-drug Interactions
Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc.

Antacids: When CIPRO XR given as a single 1000 mg dose (twice the recommended daily dose) was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible.

Omeprazole: When CIPRO XR was administered as a single 1000 mg dose concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined.

B. Pharmacodynamics

The minimum inhibitory concentrations at which 90% of organisms were inhibited (MIC_{90}) for the most common causative pathogens in Study 100275 above are as follows: *E. coli* (0.06 µg/mL); *K. pneumoniae* (0.5 µg/mL); *E. faecalis* (2.0 µg/mL); *P. mirabilis* (2.0 µg/mL); *E. aerogenes* (0.06 µg/mL), and *P. aeruginosa* (0.5 µg/mL). The MIC_{90} for other isolates of Enterobacteriaceae is <1.0 µg/mL. Urinary concentrations of ciprofloxacin towards the end of the dosing interval in subjects administered Cipro XR 1000 mg QD for 5 days, are above these MIC levels for the predominant uropathogens in both cUTI and AUP.

In addition, the clinical efficacy of Cipro XR in treating cUTI is demonstrated for *E. coli, K. pneumoniae, and E faecalis* and shown in Table 8. Three infections secondary to *P. aeruginosa* were successfully treated in the Cipro XR group with an eradication rate of 100% (3/3), and an additional patient with AUP secondary to *P. aeruginosa* was also successfully treated with Cipro XR.

TABLE 3
Bacteriological Eradication at TOC Visit (+5 to +11 Days) by Organism
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	**Cipro BID**
AUP Patients		
Escherichia coli	35/36 (97%)	41/41 (100%)
cUTI Patients		
Escherichia coli	91/94 (97%)	90/92 (98%)
Klebsiella pneumoniae	20/21 (95%)	19/23 (83%)
Enterococcus faecalis	17/17 (100%)	14/21 (67%)
Proteus mirabilis	11/12 (92%)	10/10 (100%)

IV. Clinical Review Methods

A. Structure of the Review

The primary source of data for this application is a prospective, active-controlled, randomized, double blind, multicenter Phase III trial (Study 100275).

Reviewer's Comment: According to the Draft Guidance for Industry (Complicated Urinary Tract Infections and Pyelonephritis - Developing Antimicrobial Drugs for Treatment. July 1998) a single statistically adequate and well-controlled trial establishing safety and effectiveness to an approved product should be conducted. In addition, a comparative or noncomparative trial should also be conducted.

For this application the applicant conducted a single statistically adequate and well-controlled trial. In lieu of an additional trial the Division (and the applicant) relied on previous data gathered from trials of immediate-release ciprofloxacin (tablets or oral suspension at a dose of 250 to 500 mg BID for 7 to 14 days in the treatment of mild/moderate to severe/complicated UTI.

B. Overview of Materials Utilized in the Review

Material Submitted — Electronic Data, including SAS transport files
\\Cdsesub1\n21554\N_000\2002-10-29

Material Reviewed — Electronic Data, including SAS transport files
\\Cdsesub1\n21554\N_000\2002-10-29

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested for this trial.

Reviewer's Comment: A routine DSI audit was not felt to be necessary for this NDA since Cipro XR was approved for a similar indication (NDA 21-473) on December 13, 2002. No discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

D. Evaluation of Financial Disclosure

The applicant obtained certification from each investigator and sub-investigator who enrolled patients in the Phase III study. No investigator or sub-investigator had any disclosable information to reveal.

V. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Efficacy Conclusions

The applicant conducted one pivotal Phase III trial in the United States and Canada (Protocol 100275) which documents the efficacy of Cipro XR compared to ciprofloxacin immediate release (Cipro BID) oral tablets for complicated urinary tract infection (cUTI) and acute uncomplicated pyleonephritis (AUP).

The results of supportive data provide further evidence of the efficacy of Cipro XR therapy in treatment of cUTI and AUP.

B. General Approach to Efficacy Review

The US Phase III trial (Protocol 100275) is considered pivotal. A synopsis is provided below and the complete clinical review can be found in Appendix 1.

C. Efficacy Conclusions

Cipro XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients and compared Cipro XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days). The primary endpoint for this trial is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in AUP and cUTI patients combined in the valid for efficacy (Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

There are several problems with the applicant's analysis of bacteriologic eradication in cUTI and AUP patients combined in the Per Protocol (PP) population.

- First, there is a difference in the treatment effect between patients with AUP and cUTI. The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%). In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the ciprofloxacin BID group (81.4%). The *P* value from the Breslow-Day test for treatment-by-infection interaction is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients. The Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients due to the significant treatment-by-infection interaction.

- Second, although not specified by the applicant, the Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. When the MITT population is examined along with reasons for exclusion from the PP population, there are significantly more patients in the Cipro XR group (40%, 136/342) than in the Cipro BID group (29%, 95/324) that had been excluded from the PP population. Exclusions from the PP population are primarily a result of premature discontinuations, which are primarily due to adverse events (2.9% versus 1.7%, respectively) and no valid test-of-cure (TOC) urine culture or lost to follow-up (7.7% versus 4.6%, respectively). A differential rate in exclusion may bias the results of any analysis using this population.

Therefore, the bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer and reported for both the MITT and PP populations. Since in the applicant's analysis random assignment of treatment was stratified by infection type, the calculation of the difference in eradication rates between treatment groups for each stratum alone must be adjusted for multiple comparisons (i.e., 97.5% confidence intervals). The bacteriologic eradication rates and their corresponding 97.5% confidence intervals for the differences between rates (Cipro XR minus Cipro BID) for AUP and cUTI patients, at the TOC visit are given in the following table for both the MITT and PP populations.

TABLE 4
Bacteriologic Eradication at TOC (+5 to +11 Days)
in AUP and cUTI Patients

	MITT*		PP**	
	n/N (% of Patients)	[95% CI of the Difference]	n/N (% of Patients)	[95% CI of the Difference]
AUP Patients				
Cipro XR	47/71 (66.2%)	[-26.8, 6.5]	35/40 (87.5%)	[-34.8, 6.2]
Cipro BID	58/76 (76.3%)		51/52 (98.1%)	
cUTI Patients				
Cipro XR	160/271 (59.0%)	[-13.5, 5.7]	148/166 (89.2%)	[-0.7, 16.3]
Cipro BID	156/248 (62.9%)		144/177 (81.4%)	

* Patients excluded from the Modified Intent-to-Treat group are those with no causative organism at baseline and those who did not receive study drug.

** Patients excluded from the Per Protocol group are those with no causative organism(s) at baseline, no valid TOC urine culture, inclusion/exclusion criteria violation, organism resistant to study drug, protocol violation, non-compliance with dosage regimen, did not receive study drug, inadequate duration of treatment, post-therapy antibiotics, and concomitant antimicrobial therapy.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above –10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

VI. Integrated Summary of Safety (ISS)

A. Brief Statement of Safety Conclusions

Overall, there are no clinically meaningful differences in the safety profile of Cipro XR compared to Cipro BID. Of note, however, is the difference in discontinuations due to adverse reactions in the Cipro XR group (5.4%, 28/517) compared to Cipro BID (3.7%, 19/518). The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

B. Description of Patient Exposure

A total of 1042 patients were enrolled in Study 100275 at 100 investigative centers in the US and Canada. Of the 1042 enrolled patients, 521 were assigned randomly to treatment with Cipro XR 1000 mg once daily and 521 were assigned randomly to treatment with Cipro 500 mg twice daily. Seven patients (4 in the Cipro XR group and 3 in the Cipro BID group) were not included in the valid for

safety population because study drug administration in these patients could not be documented. Thus, there were 517 (408 cUTI and 109 AUP) patients in the Cipro XR group and 518 (407 cUTI and 111 AUP) patients in the Cipro BID group valid for the analysis of safety. All patients valid for safety received treatment over the course of 5 to 15 days, with a mean duration of treatment of 12 days.

C. Specific Findings of the Safety Review

Of the 1042 patients enrolled in the study, 1035 received at least one dose of study drug and are valid for the analysis of safety (517 in the Cipro XR group and 518 in the Cipro BID group. The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups.

More patients in the Cipro XR group (28 patients or 5.4%) than in the Cipro BID group (19 patients or 3.7%) discontinued study drug due to an adverse event. The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

The most common adverse events in both treatment groups are those occurring in the digestive system [14% (71/517) for Cipro XR and 13% (67/518) for Cipro BID]. The incidence of adverse events for each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30/517) experienced at least one adverse event involving the nervous system compared with 4% (20/518) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [<1%] versus 0 patients [0%], respectively).

Most patients in both treatment groups who experienced adverse events had events that were assessed by the investigator as mild or moderate in intensity. Adverse events that occurr in at least 2% of patients treated with Cipro XR include nausea (5%), headache (3%), diarrhea (3%), vomiting (3%), dizziness (3%), dyspepsia (2%), and vaginal moniliasis (2%). Cipro BID has a similar profile of adverse events occurring in at least 2% of patients, with a slightly higher incidence of headache (5%).

Study drug-related (possible or probable relationship) adverse events were reported in 13% (68/517) of patients in the Cipro XR group and 14% (70/518) of patients in the Cipro BID group. Those occurring in 2% or more of patients in either treatment group include headache, nausea, diarrhea, dizziness, and vaginal moniliasis.

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event assessed by the investigator as severe in intensity. The number of

severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Four patient deaths were reported during the study (3 in the Cipro XR group and one in the Cipro BID group). All four patients were in the older age range (76 to 95 years), had a diagnosis of cUTI with one underlying condition, and had other concurrent medical conditions requiring concomitant medications. In all cases, the adverse event resulting in death was judged by the investigator to be of unlikely or no relationship to study drug and the FDA reviewer concurred.

Patients experiencing non-fatal serious adverse events (SAEs) is 5% in both treatment groups, (28/517 and 24/518, respectively). All SAEs reported in the Cipro XR group were judged by the investigators to be unlikely or not related to study drug.

In the two treatment groups, the incidence of clinically significant (>1.8 x ULN) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that are >3 x ULN, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients (<1%) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. In both cases, the events resolved and did not require discontinuation of study drug. Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline.

The incidence of other laboratory test abnormalities is low and comparable between the two treatment groups. Descriptive statistics of the change from baseline in laboratory test results does not reveal any trends that appear to be uniquely associated with Cipro XR treatment.

Overall, there are no clinically meaningful differences in the safety profile of either treatment on the basis of age, sex, or race.

VII. Dosing, Regimen, and Administration Issues

The dosage regimen of Cipro XR 1000 mg administered daily for 7 to 14 days for the treatment of cUTI and AUP is based on Phase I studies of this formulation and the approved labeling for conventional ciprofloxacin tablets. The current recommended dosage for ciprofloxacin tablets in the treatment of mild/moderate to severe/complicated urinary tract infections is 250 to 500 mg BID for 7 to 14 days. The Phase I studies for Cipro XR (Studies 10324 and 10339) indicate that the ciprofloxacin AUC attained following the oral administration of Cipro XR 1000 mg tablets every 24 hours is similar to the values attained following the oral administration of conventional ciprofloxacin 500 mg tablets every 12 hours (16.5 mg*h/L versus 16.0 mg*h/L, respectively, in Study 10324; and 15.4 mgh/L versus 14.8 mg*h/L, respectively, in Study 10339). The C_{max} of Cipro XR 1000 mg given every 24 hours is about 46% higher than the C_{max} for Cipro 500 mg tablets given every 12 hours.

VIII. Use in Special Populations

A. Evaluation of Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity

1. Efficacy

Age

For patients treated with Cipro XR, the bacteriologic eradication rates are lower in patients less than 65 years of age [85.0% (85/100)] compared to those 65 years of age and older [92.4% (98/106)] at the TOC visit. Less efficacy in the younger patients may be a result of the lower bacteriological response in AUP patients [87.5% 935/40] compared to cUTI patients [89.2% (148/166)]. Patients treated with Cipro XR in the AUP sub-group are younger (mean age 41 years) compared with cUTI (mean age 64 years).

Although younger patients treated with Cipro XR have lower eradication rates [85.0% (85/100)] than older patients treated with Cipro XR, the efficacy in this age group is similar to patients treated with Cipro BID [84.1% (90/107)]. Patients receiving Cipro BID responded similarly, regardless of age [84.1% (90/107) eradication for those < 65 years and 86.1% (105/122) for those ≥ 65 years].

In the Reviewer's opinion, differences seen in bacteriologic eradication between younger and older patients is not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on age.

Sex

Male patients [92.0% (81/88)] have a higher bacterial eradication rate than female patients [86.4% 102/118)] treated with Cipro XR at the TOC visit. The reverse situation is true for Cipro BID where female patients [89.8% (114/127)] have a higher eradication rate than male patients [79.4% (81/102)]. The difference in the Cipro XR group appears to be due to a higher number of female patients with superinfections and new infections.

Although the female patients treated with Cipro XR have lower eradication rates [86.4% (102/118)] than male patients treated with Cipro XR, the efficacy in this group is similar to female patients treated with Cipro BID [89.8% (114/127)] and higher than male patients treated with Cipro BID [79.4% (81/102)].

In the Reviewer's opinion, differences seen in bacteriologic eradication between male and female patients is not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on sex.

Race
Most of the valid for efficacy patients are Caucasian [79% (345/435)]. Among patients who are not Caucasian, most are categorized as Black or Hispanic [20% (88/435)]. Less than 1% of patients in each treatment group are Asian. Bacteriologic eradication rates for both Cipro XR and Cipro BID appear similar for Caucasian and Black patients at the TOC visit. Hispanic patients appear to have higher eradication rates. There are too few Asian patients in the study to make an assessment on eradication.

In the Reviewer's opinion, differences seen in bacteriologic eradication between Caucasian, Black, and Hispanic patients are not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on race.

2. Safety

Age
The overall incidence rates of adverse events are similar across age groups (< 65 years, 65-74 years, and ≥ 75 years) in patients within each treatment group. For both the Cipro XR and Cipro BID group, patients aged 65-74 years experienced nausea less frequently than those younger or older. More patients younger than 65 years of age in the Cipro XR group reported vomiting [4% (12/271)] than did patients in the same age category treated with Cipro BID [<1% (2/255)]. The incidence of dizziness in patients 75 years of age or older is slightly higher in the Cipro XR group [4% (6/149)] as compared to the Cipro BID group [1% (2/159)]. The incidence rates of other adverse events for both treatment groups across age groups are similar.

In the Reviewer's opinion, differences seen in adverse events between younger and older patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by age in the product labeling.

Sex
Within each sex, the event rates are similar between Cipro XR and Cipro BID patients. Overall, female patients have higher event rates than male patients [34% (102/298) for females vs. 29% (102/299) for males]. Overall, female patients have higher rates of nausea and diarrhea [nausea: 6% in both Cipro XR (19/298) and Cipro BID (18/299) groups; diarrhea: 4% (11/298) in Cipro XR and 3% (8/299) in Cipro BID] than the male patients [nausea: 2% in both Cipro XR (5/219) and Cipro BID (5/219) groups; diarrhea: 2% (4/219) in Cipro XR and 1% (3/219) in Cipro BID). Of the Cipro XR treated patients more females reported vomiting [4% (12/298)] than males [<1% (2/219)].

In the Reviewer's opinion, differences seen in adverse events between male and female patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by sex in the product labeling.

Race
Adverse event rates generally are consistent across subgroups. The number of patients with any adverse event is comparable between the two treatments for Caucasian: 31% (129/410) for Cipro XR and 33% (138/414) for Cipro BID

and Hispanic 27% (13/48) for Cipro XR and 30% (16/53) for Cipro BID patients. Black patients treated with Cipro XR have a higher incidence of adverse events [38% (21/55)] compared with Black patients treated with Cipro BID [23% (11/48)]. This is due primarily to adverse events attributed to the urogenital system: 16% (9/55) in Cipro XR-treated patients versus 8% (4/48) Cipro BID-treated patients.

Within the Cipro XR group, more Hispanic patients developed nausea, headache, or vomiting than did black or Caucasian patients. In the Cipro BID group, Hispanic patients have a higher incidence of abdominal pain than did patients of the other two racial groups. There are no other notable differences between the two treatment groups by race. Overall, there are no clinically meaningful differences in the incidence of adverse events across the three racial groups (i.e., Caucasian, Black, and Hispanic). Conclusions cannot be made for patients categorized as Asian or American Indian because their numbers are too small for a meaningful comparison.

B. Pediatric Program

Pursuant to 21 CFR 314.55 (c), the applicant requests a full waiver of the assessment of the efficacy and safety of Cipro XR 1000 mg tablets in the pediatric population.

Cartilage lesions have been demonstrated in the weight bearing joints of immature dogs given ciprofloxacin. This is a class effect of all quinolones. The warnings section of the proposed package insert cautions against the use of this product in pediatric patients. The applicant believes that definitive statements concerning the manifestation of this effect in humans cannot be made presently.

(b) (4)

Ciprofloxacin is an extremely bitter drug substance. The applicant states that development of an oral liquid formulation for twice daily dosing was extremely difficult, and they believe that "reasonable attempts", to produce an oral liquid formulation for once-daily dosing at this strength would be impossible. In addition, Cipro XR tablets are quite large. They believe a smaller once daily tablet for the pediatric population will still be too large for many children to swallow. Finally, they do not believe the development of such a smaller tablet will provide a "meaningful therapeutic benefit" for pediatric patients over existing treatments, as there already exists an oral liquid dosage form of ciprofloxacin available for use for pediatric patients.

In summary, the applicant requests a full waiver for the assessment in pediatric patients for Cipro XR (NDA 21-554). (b) (4)

Reviewer's Comment: The FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court and on October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling.

C. Data in Other Populations

Pediatric patients (< 18 years) and patients with significant renal impairment (serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/min*1.73 m^2) or hepatic impairment (baseline SGOT or SGPT and/or total bilirubin greater than 3 times the upper limit of normal), and pregnant women were excluded from the Cipro XR development program. Therefore it is not possible to comment on the efficacy or adverse event profile in these populations.

IX. Conclusions, Recommendations, and Labeling

A. Conclusions Regarding Efficacy and Safety

In this submission, the applicant demonstrates the activity of 7 to 14 days of treatment with 1000 mg of Cipro XR in the treatment of patients with complicated urinary tract infection (cUTI) and acute pyelonephritis (AUP). The efficacy of Cipro XR is compared to a FDA-approved regimen consisting of immediate-release ciprofloxacin 500 mg tablets twice daily (Cipro BID) for 7 to 14 days. The Cipro BID regimen is an acceptable comparator since it is approved for severe/complicated urinary tract infections at a dose of 250 to 500 mg twice daily for 7 to 14 days.

B. Recommendations on Approvability

In summary, Cipro XR is safe and effective for the treatment of patients with cUTI in patients with susceptible organisms, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* [a], and *Proteus mirabilis*. In addition, Cipro XR is safe and effective for the treatment of patients with AUP in patients with susceptible organisms, including *Escherichia coli*. The recommendation is for approval of Cipro XR 1000 mg once daily for 7 to 14 days for cUTI and AUP.

[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

C. Labeling

1. Changes to Applicant's Proposed Label

The major labeling changes and means of resolution are indicated below by affected section(s) of the label:

Microbiology, Indications and Usage, and Clinical Studies

The applicant originally included (b) (4) and *Pseudomonas aeruginosa* in the "Indications and Usage" section and in the efficacy table in the "Clinical Studies" section of the package insert. At a teleconference on July 10, 2003, the Division asked the applicant to provide information to support the inclusion of these two organisms in the table, since there are less than 10 isolates for each. On July 29, 2003 the applicant submitted the requested information. They indicated that they were withdrawing the proposal to include (b) in the "Indications and Usage" and "Clinical Studies" section and will shift the organism to the "second list" in the "Microbiology" section of the package insert.

Regarding the inclusion of *P. aeruginosa* in the XR label, the applicant justified their position with data to support the following: (1) immediate-release (IR) ciprofloxacin is indicated for cUTIs, including those caused by susceptible strains of *P. aeruginosa*, (2) an antimicrobial agent selected to treat cUTI should achieve adequate concentrations at the site of infection. Cipro XR 1000 mg tablets have an absolute bioavailability of up to 90% and a relative bioavailability of 98% when compared to the IR formulation. Plasma concentrations are about 40% to 70% greater than the concentrations achieved with 500 mg BID of the immediate-release formulation. In the urine, the XR formulation of ciprofloxacin (1000 mg) achieves significantly higher concentrations of ciprofloxacin than the immediate release formulation (500 mg BID) for up to 12 hours following a dose. Concentrations of both formulations in the urine remain in excess of the MIC values of susceptible pathogens throughout the dosing interval, (3) surveillance data shows that 75% of *P. aeruginosa* isolates from UTIs analyzed between Jan 1st and December 31st 2002, were susceptible to ciprofloxacin, and (4) nine of the 14 *P. aeruginosa* isolates identified in the pivotal trial (100275) were susceptible to ciprofloxacin. All nine were clinically cured and bacteriologically eradicated.

The applicant concludes that a combination of the microbiological data (MICs) for susceptible isolates of *P. aeruginosa* along with the achievable concentrations of the drug in plasma and urine, supports Cipro XR as an appropriate drug to select for the treatment of cUTI caused by susceptible strains of *P. aeruginosa*.

The applicant also indicated that they would be amenable to conduct a Phase IV study to gather additional isolates of *P. aeruginosa*, similar to what the Division requested of the applicant when the Division approved *Staphylococcus saprophyticus* in uUTI (Cipro XR 500 mg, NDA 21-473), if the Division would grant them *P. aeruginosa* in the label.

The reviewer accepts the applicant's rationale for inclusion of *P. aeruginosa* in the label, based on the pharmacokinetic and susceptibility data provided. In addition, the applicant will be requested to obtain information on additional isolates of *P. aeruginosa* as a Phase IV commitment.

Adverse Events

The applicant originally proposed combining the data in the adverse events section for the 500 mg and 1000 mg XR tablets. The rate of adverse events leading to discontinuation was reported as 1.8%, which is an average of 0.2% for the 500 mg XR tablet and 2.3% for the 1000 mg XR tablet. Therefore, the reviewer requested the applicant report the rates of discontinuation due to AEs and the most common AEs leading to discontinuation separately for the two doses. The rationale behind this request is that the patient populations (i.e., uUTI versus cUTI/AUP), duration of treatment (3 days versus 7-14 days), as well as treatment doses (500 mg versus 1000 mg) are different and may be contributing to the difference in discontinuation rates. In addition to separating the information by dose and indication, the applicant was asked to include information on discontinuation due to AEs from the comparator arms (i.e., ciprofloxacin immediate release 250 mg BID and 500 mg BID, respectively).

Clinical Trials

The description of the pivotal study (100275) was modified by the reviewer from the applicant's proposal in three ways:

- In the trial there are a disproportionate rate of exclusion from the PP population for the two treatment groups. The Division feels the results of the MITT analysis should be represented in the label to adequately describe the study. Therefore, results of the MITT analysis are included, in addition to the PP analysis proposed by the applicant.

- In the trial there is also a significant treatment by infection interaction, such that the Division does not consider it appropriate to pool bacteriologic results for the cUTI and AUP subgroups. Therefore, bacteriologic eradication rates, and corresponding confidence intervals, in both the MITT and PP populations are reported separately for the cUTI and AUP subgroups and not reported for the combined sub-groups, as proposed by the applicant. The Division allowed the clinical success rates to be reported for the combined cUTI and AUP subgroups, in the PP population, because there was no significant treatment by infection interaction for this endpoint.

- Cipro XR achieves lower rates of bacteriologic eradication in the AUP subgroup and higher rates in cUTI subgroup compared to Cipro BID. By definition, in this study bacteriologic failures include patients with persistence, new infections, and superinfections. Therefore, a narrative descriptions of the number of patients failing due to persistence, new

infection, or superinfection and the causative pathogen(s) are added for AUP and cUTI patients in the PP population.

2. Other Potential Labeling Issues Related to Safety

Three potentially serious adverse events (occcuring in less than 1% of patients) have been added to the label. These adverse events were not seen with the 500 mg XR dose and are as follows: "liver function tests abnormal", "bradycardia", and "syncope". In order to determine the clinical relevance of the event, the reviewer investigated each AE. Patient summaries/narratives are included below. The reviewer does not feel that these adverse events are clinically relevant and also do not represent a "signal" for more serious cardiac or hepatic toxicity.

- Liver Function Tests Abnormal: Two patients in the Cipro XR group had liver function test abnormalities that were reported as adverse events. For one patient the liver enzyme levels were below 1.8x ULN and were thought to be possibly related to study drug. In the other patient the liver enzyme levels were 3x ULN and 4.8x ULN for SGOT and SGPT, respectively, and not believed to be related to study drug. In both cases, the events resolved and did not require discontinuation of study drug.

- Bradycardia: A 20-year-old male patient had a past medical history of a C6-7 spinal cord injury, and intermittent bradycardia, since his the injury 3 months earlier. On the second day of study drug treatment, he experienced bradycardia, dizziness and double vision. The study drug was immediately discontinued and IV fluids (D5W, 0.45NS) were administered in the office for the bradycardia. All three events resolved the next day and were considered possibly related to study drug.

- Syncope: On the first day of study drug treatment a 72-year-old female patient reported lightheadedness. No action was taken and the event resolved that day. Three days later, she experienced a faint feeling. The study drug was permanently discontinued and the event improved. This patient withdrew consent for further treatment. Both events were considered possibly related to study drug.

_____

Joette M. Meyer, Pharm.D.
Clinical Reviewer, DSPIDP, ODE IV, CDER

Concurrence:
HFD-590/TLMO/RocaR
HFD-590/DivDir/AlbrechtR

APPENDIX 1 – INDIVIDUAL STUDY REVIEW FOR STUDY 100275

Title
Prospective, Randomized, Double Blind, Multi-Center Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once-Daily (QD) [redacted] (b) (4) Tablets 1000mg versus Conventional Ciprofloxacin 500mg Tablets BID in the 7-14 Day Treatment of Patients with Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis (AUP).

*The product was subsequently renamed Cipro XR

Protocol Number
100275

Study Initiation
April 15, 2001

Study Completion
July 11, 2002

All the following tables in this review are reproductions from the applicant's submission, unless otherwise noted.

I. Investigators and Study Administrative Structure

This is a multicenter study involving 100 investigative sites in the United States and Canada. The study was monitored by a contract research organization (CRO), [redacted] (b) (4) in accordance with GMP guidelines and Standard Operating Procedures (SOP) for Bayer and [redacted] (b) (4). Monitoring visits were done to ensure compliance with the protocol, to review source documents and case report forms (CRF), and to assess drug accountability.

Analysis of routine blood, serum pregnancy, and urine laboratory samples, urine cultures, and susceptibility testing were processed and analyzed at [redacted] (b) (4)
Screening urine pregnancy tests for women of childbearing potential were conducted at the study sites.

The design for the pivotal study was guided by following two FDA documents:

- Points to Consider: Urinary Tract Infections. 1997
- Draft Guidance for Industry: Complicated Urinary Tract Infections and Pyelonephritis - Developing Antimicrobial Drugs for Treatment. July 1998

The applicant also gave consideration to the other following documents when designing this study: the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines (1993), the Committee on Proprietary Medicinal Products' (CPMP) Note for Guidance on Evaluation of New Antibacterial Medicinal Products (1998), and the Infectious Disease Society of America (IDSA) Practice Guidelines Committee publication (1999).

II. Study Objectives

The primary objective of this study is to determine if ciprofloxacin extended-release (Cipro XR) 1000 mg orally once daily for 7 to 14 days is non-inferior to immediate-release ciprofloxacin (Cipro) 500 mg orally twice daily for 7 to 14 days in the treatment of patients with complicated urinary tract infection (cUTI) or acute uncomplicated pyleonephritis (AUP). The primary efficacy variable is bacteriological outcome at the test-of-cure (TOC) visit (+5 to +11 days after the last dose of study drug)

Secondary objectives are to compare the clinical response rate between treatments at the TOC visit, and to compare bacteriological and clinical response rates at the late follow-up visit (+28 to +42 days after the last dose of study drug).

III. Investigational Plan

This is a prospective, randomized, double blind, multicenter, Phase III clinical trial conducted at 100 investigative centers in North America. Men and non-pregnant women who were 18 years of age or older and who had a cUTI or AUP were eligible for enrollment. A total of 1036 consenting qualified patients were expected to participate in order to obtain 202 evaluable patients in each treatment arm.

Reviewer's Comment: The original protocol specified a total of 408 patients required for enrollment in order to obtain 153 evaluable patients in each treatment arm. Protocol Amendment 1 changed these numbers to 886 patients and 332, respectively. Protocol Amendment 5 increased the total number of patients enrolled to 948 to obtain 237 evaluable patients per treatment arm. Finally, Protocol Amendment 7 increased the numbers to 1036 patients total and 202 evaluable patients per arm.

After meeting all inclusion/exclusion criteria and providing written informed consent, patients were stratified based on diagnosis (Stratum I: acute uncomplicated pyelonephritis; Stratum II: complicated UTI) and assigned randomly to treatment with either Cipro XR 1000 mg once daily or Cipro 500 mg twice daily for 7 to 14 days.

Patient assessments were performed at the following visits:

- Screening visit (within 48 hours before the first dose of study drug);
- During-therapy visit (Day 3 to 5 of therapy)
- TOC visit (Day +5 to +11 post-treatment)
- Late follow-up visit (Day +28 to +42 post-treatment)
- If applicable: premature-discontinuation-of-study-drug visit, or a post-alternative-treatment visit (Day +2 to +4 post-treatment).

The efficacy of the study drug was determined at the TOC visit on the basis of the clinical and bacteriological outcome of the patient.

The clinical outcome was based on serial examinations of the patient to determine the effect of therapy on the signs and symptoms of the infection. All pertinent laboratory tests or procedures that reflect the course of the urinary tract infection (UTI) were also assessed. Absence or reduction of pyuria, dysuria, frequency,

urgency, suprapubic pain, fever (>38°C/100.4°F orally), chills, flank pain, nausea and/or vomiting, or costo-vertebral angle (CVA) tenderness on examination were used to assess the clinical response.

The bacteriological outcome was based on the results of urine cultures obtained before the start of therapy, at the TOC visit, at the late follow-up visit and at premature discontinuation (if applicable). The safety of study drug treatment was monitored by clinical observations including the determination of vital signs, adverse event monitoring, and laboratory assessments of hematologic, liver, and renal functions.

IV. Inclusion Criteria

- Men or non-pregnant women, 18 years of age or older, with a suspected cUTI or AUP.

- Women of childbearing potential must use two highly reliable methods of contraception during exposure to study drug (e.g., if a woman is on oral contraceptive, she is required to use a barrier method of contraception as well).

- For cUTI, patients must present with one or more of the following signs or symptoms:
    - dysuria
    - urgency
    - frequency
    - suprapubic pain
    - back pain
    - flank pain
    - CVA pain and tenderness
    - fever (>38° C/100.4° F orally) with or without chills

  AND at least one or more underlying conditions, such as:
    - indwelling urinary catheter
    - 100 mL of residual urine after voiding
    - neurogenic bladder
    - obstructive uropathy due to nephrolithiasis, tumor or fibrosis
    - urinary retention in men, possibly due to benign prostatic hypertrophy

- For AUP, patients must present with clinical signs and symptoms of an ascending UTI, manifested by all 3 of the following: fever (>38°C/100.4°F orally), chills and flank pain.

  In addition, patients also may have CVA tenderness and nausea. Symptoms of lower UTI such as dysuria, nocturia, frequency, urgency, suprapubic or lower back pain also may be present.

- Patients also must have a positive pre-treatment, clean-catch, midstream urine culture, defined as $\geq 10^5$ CFU/mL for a causative pathogen, within 48 hours of enrollment.

If more than 1 pathogen is identified, each should be present at a colony count $\geq 10^5$ CFU/mL to be included in the analysis. In catheterized patients, the urine sample may be obtained from the catheter using a sterile technique and not from the Foley bag. In addition, patients should have blood culture specimens (two sets from different sites) obtained simultaneously with the urine specimen at the time of enrollment. If two or more pathogens grow at $\geq 10^5$ CFU/mL from the baseline urine culture sample of a catheterized patient, all isolates will be considered to be contaminants (i.e., nonevaluable), unless the same pathogen is isolated from a simultaneously obtained blood culture sample. If the same pathogen grows in the urine at $\geq 10^5$ CFU/mL and also is isolated from the blood, then it will be considered to be an evaluable pathogen.

- Patients must also have pyuria, defined as ≥10 leukocytes/mm^3 in unspun pre-treatment urine specimens or >5 WBC/hpf in spun pre-treatment urine specimens. The sedimentation method or slide method of assessing urinary leukocytes is acceptable. The causative pathogen must be susceptible to ciprofloxacin as determined by *in vitro* susceptibility testing.

V. Exclusion Criteria

Patients will not be enrolled if they:

- Have a history of allergy to quinolones
- Are unable to take oral medication
- Have prostatitis or epididymitis
- Have an intractable infection requiring >14 days of therapy
- Have an uncomplicated UTI
- Have a renal transplant
- Have ileal loops or vesico-ureteral reflux
- Have a ciprofloxacin-resistant pathogen upon urine or blood culture
- Have received systemic antimicrobial therapy within 48 hours prior to enrollment
- Have a neutrophil count <1000/mm^3, CD4 <200/mm^3 or other conditions associated with significant depression in host defense (HIV testing was not mandatory)
- Have a requirement for concomitant systemic antibacterial therapy with agents not specified in this protocol
- Have significant liver impairment (baseline SGOT or SGPT and/or total bilirubin) greater than 3 times the upper limit of normal
- Have significant renal impairment (serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/min*1.73 m^2)
- Have a history of tendinopathy associated with fluoroquinolones;
- Are pregnant, nursing or in whom pregnancy could not be excluded or unreliable contraception was being used; diagnosed with a rapidly fatal underlying disease (death expected within 6 months)
- Have a requirement for concomitant administration of sucralfate or divalent and trivalent cations, such as iron or antacids containing magnesium, aluminum or calcium; previously enrolled in this clinical study; taken an investigational drug in the last 30 days.

VI. Patient Removal

A patient may have been withdrawn from the study at any time at the discretion of the investigator or if a patient withdrew consent. If a patient did not show improvement after three days (i.e., therapeutic failure), if a serious toxic or allergic reaction occurred, or if a superinfection developed, study drug therapy was discontinued and appropriate alternative therapy was instituted. Before alternative antimicrobial drugs were given, however, the patient was fully evaluated and appropriate laboratory tests including cultures were performed. In addition, the investigator may have withdrawn patients from the trial for reasons such as poor compliance (taking < 80% of study medication), an elevated pre-treatment laboratory test result, deterioration in a concurrent clinical condition precluding continuation of study medication, or protocol violation.

The study could be terminated if, in the opinion of the investigator and/or sponsor, continuation would represent an unacceptable risk to the patients, or if the status of ciprofloxacin XR development by the sponsor had changed such that the study would no longer be a necessary part of the clinical program.

If, during the course of study drug therapy, study drug was discontinued prematurely for any reason, a premature discontinuation of therapy visit was required. All end-of-therapy assessments were to be performed at this visit. In addition, a clean-catch midstream urine sample was to be obtained and sent to the central laboratory for culture and susceptibility testing.

VII. Treatments and Blinding

Patients received Cipro XR 1000 mg tablets orally once daily or Cipro 500 mg tablets orally twice daily for 7 to 14 days. Study medication was provided in a package containing 2 bottles to maintain the double blind design of the study.

Bottle #1 (the smaller bottle): 14 tablets of Cipro XR 500 mg or matching placebo
Bottle #2 (the larger bottle): 28 tablets of Cipro 500 mg or matching placebo

For the first daily dose the patient was instructed to take 2 tablets: one tablet from Bottle #1 and one tablet from Bottle #2. For the second daily dose the patient was instructed to take one tablet from Bottle #2 and none from Bottle #1. Thus, in a 24-hour dosing period, the patient took a total of 3 tablets.

All doses of study medication were to be taken with at least 120 mL (4 oz.) of water and without regard to meals.

All personnel associated with drug administration (including study and treating health care providers), patients, study monitors, and Bayer medical research personnel were blinded to the treatment assignment.

In the event of an emergency, the random code could be broken; however, the investigator was instructed to make every attempt to contact Bayer prior to breaking the code. If the code was broken, Bayer was notified by telephone or facsimile within 48 hours. Regardless of the reason, once the blind for any patient was broken, that patient was not valid for the primary efficacy analysis. In the event the blind was

broken, the date and reason for the code break was documented and signed by the investigator in a report to the applicant.

VIII. Method of Patient Assignment to Treatment Group

Patients who met all enrollment criteria were stratified based on the presence or absence of AUP as follows:

Stratum I: Patients with acute uncomplicated pyelonephritis
Stratum II: Patients without acute uncomplicated pyelonephritis but with a diagnosis of cUTI

Following stratification, patients were assigned randomly to one of two drug treatment groups (i.e., Cipro XR 1000 mg once daily or Cipro 500 mg twice daily) in accordance with a computer-generated random code provided by the applicant. Patients were assigned from a single stream code of study numbers. The investigators, study monitors, and patients all were blinded to the random code assignment.

Randomization and initiation of study drug treatment is permitted before the culture report became available.

Reviewer's Comment: In order to obtain an indication for AUP, in addition to cUTI, an adequate number of AUP patients must be studied. According to the Draft Guidance for Industry, the minimum number of AUP patients required is 30 patients per investigational treatment per study. In this study, there are 40 AUP patients in the valid for efficacy population treated with Cipro XR. Therefore, the applicant is eligible to receive an AUP indication based on number of patients. In addition, minimum efficacy requirements for Cipro XR will need to be met.

IX. Concomitant Therapy

Patients were not enrolled in the study if they had received systemic antimicrobial therapy within 48 hours before enrollment.

Non-study antibacterial agents were not be administered during the study period, from enrollment through completion of the late follow-up visit (+28 to +42 days post-treatment) unless patients were considered treatment failures or clinical relapses.

Efforts were made to minimize the use of concomitant medications of any kind during the duration of study medication administration.

Patients requiring treatment with sucralfate or divalent and trivalent cations, such as iron, multivitamin preparations, or antacids containing magnesium, aluminum, or calcium, were instructed take such medications six or more hours before or two or more hours after the dose of study drug.

Patients on concomitant therapy with warfarin or theophylline were only included in the study if provision was made to monitor for adequate coagulation parameters and theophylline levels during the study.

All concomitant medications were recorded by the investigator.

X. Treatment Compliance

Patients were instructed to bring their study medication bottles with them to the during-therapy visit (Day 3 to 5) and TOC visit (Day +5 to +11). If a patient failed treatment or discontinued study drug therapy prematurely, unused medication was to be returned at the visit at which this occurred. In order to document patient compliance, a count of any unused study drug was recorded. Patients who had taken ≥ 80% of the scheduled doses were considered to be compliant with the study protocol.

XI. Efficacy and Safety Assessments

All study procedures are summarized in the Trial Flow Chart shown in Table 1.

TABLE 1
Trial Flow Chart

Activity	Pre-Rx[a]	During Therapy (Day 3-5)	Test-of-Cure (Day +5 to +11)	Premature D/C of Rx (if applicable)	Post-Alternative Rx (if applicable) (Day +2 to +4)	Late Follow-Up Visit (Day +28 to +42)
Evaluation of patient eligibility/medical history/health status	X					
Physical examination	X					
Brief interval physical examination/Vital signs		X	X	X	X	X
Obtained signed informed consent	X					
Pregnancy test (urine/serum)[b]	X		X	X		
Pyuria measurement	X	X	X	X		X
Clean-catch midstream urine specimen: culture, colony count, susceptibility test, urinalysis	X	X	X	X		X
Blood cultures	X	X[c]				
CBC/platelets/ blood chemistry, Theophylline/PT[d]	X	X	X	X		
Clinical assessment	X	X	X	X	X	X
Assessment of patient compliance with study medication dosing regimen		X	X	X		
Monitor Adverse Events[e]		X	X	X	X	X

[a] Within 48 hours before onset of drug therapy.
[b] Patients may be enrolled on the basis of a negative urine pregnancy test performed in the clinic. A serum pregnancy test also must be sent to the central laboratory.
[c] If initial blood culture yield pathogen(s); blood cultures should be repeated until the results are negative.
[d] Theophylline levels or PT (for warfarin) are performed only if patients are taking these medications.
[e] Adverse events are reported through day +5 to +11 post-treatment. Serious adverse events and deaths will be reported through day +28 to +42 post-treatment as the investigator became aware of them.

XII. Efficacy Assessments

A. Bacteriologic Outcome

The bacteriological outcome was based on the results of urine cultures performed before the start of therapy, at the TOC visit (+5 to +11 days post-treatment), and at the late follow-up visit (+28 to +42 days post-treatment) or premature discontinuation visit (if applicable). All urine specimens were processed for culture and susceptibility testing by a central laboratory. Urine specimens for culture were obtained by the mid-stream clean-catch urine technique or by catheterization and a quantitative count was performed by the central laboratory.

Reviewer's Comment: The pimary efficacy endpoint is eradication of the baseline pathogen at the TOC visit (+5 to +11 days post-treatment). All other outcomes described below (i.e., persistence, superinfection, new infection, and indeterminate) are considered failures by the applicant.

1. TOC visit (Day +5 to +11 post-treatment)

The bacteriological outcome at the TOC visit was graded as follows:

Eradication: A urine culture, obtained within the Day +5 to +11 post-treatment window, showing that all uropathogens found at study entry in a quantity of $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL.

Persistence: A urine culture, obtained any time after the completion of therapy, grew $\geq 10^4$ CFU/mL of the original uropathogen.

Superinfection: A urine culture grew $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active therapy.

New infection: A pathogen other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/mL, was present at a level $\geq 10^5$ CFU/mL anytime after treatment was completed.

Indeterminate: It was not possible to determine bacteriological outcome. The reason for an indeterminate evaluation should be documented.

Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation.

2. Late follow-up visit (Day +28 to +42 post-treatment)

The bacteriological outcome at the late follow-up visit was graded as follows:

Continued eradication: Causative organism(s) present in numbers $<10^4$ CFU/mL at the TOC visit and at the late follow-up visit.

Persistence: Causative organism(s) $\geq 10^4$ CFU/mL noted at the TOC visit, regardless of the results of the culture at the follow-up visit, were carried forward.

Superinfection: Growth $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active study drug therapy, with symptoms of infection as previously stated.

Recurrence: Causative organism(s) in numbers $< 10^4$ CFU/mL at the TOC, but reappearance of the same organism(s) $\geq 10^4$ CFU/mL before or at the Day +28 to +42 post-treatment visit.

New infection: A pathogen other than the original microorganism isolated at baseline at a level of $\geq 10^5$ CFU/mL was present at a level $\geq 10^5$ CFU/mL anytime after treatment was finished.

Indeterminate: Bacteriological outcome could not be evaluated for any reason (e.g., post-treatment culture was not obtainable). The reason for an indeterminate evaluation must have been documented.

3. Premature discontinuation

The bacteriological outcome at premature discontinuation (if applicable) was graded as follows:

Eradication: A urine culture performed before alternative antimicrobial therapy showed that all uropathogens found at study entry in a quantity $\geq 10^5$ CFU/mL were reduced to $< 10^4$ CFU/mL.

Persistence: A urine culture performed any time after premature discontinuation of therapy grew $\geq 10^4$ CFU/mL of the original uropathogen.

New infection: A pathogen other than the original microorganism isolated at baseline at a level $\geq 10^5$ CFU/mL was present at a level $\geq 10^5$ CFU/mL anytime after treatment was prematurely discontinued.

Indeterminate: It was not possible to determine bacteriological outcome. The reason for an indeterminate evaluation must have been documented.

B. Clinical Outcome

The clinical outcome was based on serial examinations of the patient to determine the effect of therapy on the signs and symptoms of the infection. All pertinent laboratory tests or procedures that reflected the course of the UTI also were assessed. Absence or reduction of pyuria, dysuria, frequency, urgency, suprapubic pain, fever (>38°C/100.4°F orally), chills, flank pain, nausea and/or vomiting, and CVA tenderness on examination were used to assess the clinical response. At each evaluation, each of the clinical signs and symptoms were assigned a severity score from 0 (none present) to 3 (severe).

1. **During therapy visit (Day 3-5)**

   The clinical outcome at the during-therapy visit was graded as follows:

   Clinical improvement: A sufficient reduction in the severity and/or number of signs and symptoms of infection such that the patient could continue taking study medication to completion of 7 to 14 days of therapy.

   Clinical failure: An insignificant change or worsening of signs and symptoms such that study medication could not be continued or initiation of alternative antimicrobial therapy was required.

   Indeterminate: It was not possible to determine clinical outcome (e.g., <3 days of study drug exposure because of premature discontinuation due to an adverse event). The reason for an indeterminate evaluation must have been documented.

2. **TOC visit (Day +5 to +11 post-treatment)**

   The clinical outcome at the TOC visit was graded as follows:

   Clinical cure: Resolution or improvement of signs and symptoms at the TOC visit such that no additional antimicrobial therapy was administered or required.

   Clinical failure: No apparent response to therapy, persisting signs and symptoms of infection, reappearance of signs and symptoms at or before the TOC visit, or the use of additional antimicrobial therapy was necessary for the current infection.

   Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented. Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation.

3. **Late follow-up visit (Day +28 to +42 post-treatment)**

   Clinical outcome at the late follow-up visit for those patients who did not receive alternative antimicrobial therapy at the TOC visit was graded as follows:

   Continued clinical cure: Continued disappearance of acute signs and symptoms of infection or continued improvement such that alternative antimicrobial therapy was not required or administered.

   Failure: An outcome of failure was carried forward from the TOC visit (Day +5 to +11 post-treatment).

   Relapse: Reappearance of signs and symptoms of the current infection considered to be related to an infectious (bacterial) process such that initiation of alternative antimicrobial therapy was required.

Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented.

4. Premature discontinuation

Clinical outcome at premature discontinuation (if applicable) was graded as follows:

Clinical cure: Resolution or improvement of signs and symptoms at the time of discontinuation such that no additional antimicrobial therapy was administered or required.

Clinical failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at the time of discontinuation; or the use of additional antimicrobial therapy is necessary for the current infection.

Indeterminate: It was not possible to determine clinical outcome. Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation. The reason for an indeterminate evaluation must have been documented.

5. Post-alternative antimicrobial therapy (Day +2 to +4 post-alternative antimicrobial therapy)

The clinical outcome for those patients who received alternative antimicrobial therapy was graded as follows:

Clinical cure: Resolution or improvement of signs and symptoms at the end of alternative antimicrobial therapy such that no additional antimicrobial therapy was administered or required.

Clinical Failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before this visit requiring alternative antimicrobial therapy for the infection.

Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented.

C. Safety Assessments

The safety parameters evaluated were clinical adverse events, blood chemistry and hematology, urinalysis, theophylline levels and prothrombin time (if applicable), and a pregnancy test before treatment (urine test with confirmation by a serum pregnancy test), at the TOC visit, and at the time the drug was prematurely discontinued (if applicable). Each patient was carefully monitored for adverse events, including clinical laboratory test variables.

The definition of an adverse event was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product,

and which did not necessarily have to have a causal relationship (association) with this treatment. The adverse event may be: a new illness; worsening of a sign or symptom of the condition under treatment or of a concomitant illness; an effect of the study medication; an effect of the comparator drug; an effect related to study procedure; or a combination of 1 or more of these factors.

A laboratory test result that was abnormal or represented a clinically significant change from baseline was to be recorded as an adverse event if any of the following conditions was met: it resulted in discontinuation of treatment with study drug; there were clinical manifestations; treatment was required; or the investigator believed the event to be relevant. Each event was to be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken, and outcome.

An assessment was made of the seriousness, intensity, and relationship of the adverse event to the administration of the study medication. Adverse events were reported through the TOC visit. Patients who experienced adverse events during the study were to be followed until the events either resolved or stabilized.

A complete physical examination was conducted at the pre-therapy visit. Interval physical examinations, including vital signs, were conducted at the during-therapy visit (Day 3 to 5), TOC visit (Day +5 to +11 post-treatment) and the late follow-up visit (Day +28 to +42 post-treatment) or, if applicable, the premature discontinuation visit, and the post-alternative antibiotic visit (+2 to +4 days post-treatment).

Blood and urine samples were obtained from each patient for safety purposes at the pre-therapy and TOC visits, and if applicable, the premature discontinuation visit. Specimens for laboratory testing could also be obtained during therapy if deemed necessary by the investigator. The laboratory safety variables evaluated in this study included the following:

Hematology: hemoglobin; hematocrit; white blood cell (WBC) count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils); and platelet count; and prothrombin time (PT) and INR (only for patients receiving concomitant warfarin).

Serum chemistry: alanine transaminase (ALT/SGOT), aspartate transaminase (AST/SGPT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, serum creatinine, blood urea nitrogen (BUN), uric acid, amylase, gamma glutamyl transpeptidase (GGT), and serum glucose. In addition, theophylline serum concentrations for any patients receiving concomitant theophylline, and serum pregnancy test for women of childbearing potential.

Urinalysis: Semiquantitative and microscopic examination for appearance, specific gravity, leukocytes, blood/erythrocytes, nitrites, protein, pH, ketones, bilirubin, and glucose. For women of childbearing potential, a urine pregnancy test was performed at the investigative site, which was confirmed by a serum pregnancy test.

XIII. Statistical and Analytical Plan

A. Analysis Populations

1. Valid for Efficacy (i.e., Per Protocol) Population

The primary population for analysis was specified as the population of patients valid for efficacy. For a course of therapy to be judged valid for evaluating the primary efficacy parameter (i.e., bacteriological outcome at the TOC visit), the following criteria must have been met:

- A diagnosis of complicated UTI must have been confirmed before treatment on the basis of the presence of signs and symptoms consistent with a lower UTI, with underlying conditions as noted in the inclusion criteria or a diagnosis of AUP must have been confirmed on the basis of the presence of fever (>38°C/100.4°F orally), chills, and flank pain, and a positive urine culture, with recovery of a causative organism(s) present in a quantity $\geq 10^5$ CFU/mL.

- For patients with indwelling catheters, if two or more pathogens grew from the baseline urine culture, all isolates were considered to be contaminants (i.e., unevaluable), unless the same pathogen was also isolated from a simultaneously obtained blood culture specimen. If the same pathogen grew in the urine at $\geq 10^5$ CFU/mL and was isolated from the blood, then it was considered to be an evaluable pathogen.

- All inclusion/exclusion criteria must have been met.

- The study drug must have been administered for a minimum of 3 days if the treatment result was failure or a minimum of 7 days if the treatment result was success.

- Bacteriological outcome must have been determined at the TOC visit (Day +5 to +11 post-treatment) unless the patient's outcome was early treatment failure. An indeterminate designation at the TOC visit invalidated the patient data for efficacy evaluation.

- No other systemic antibacterial agent must have been administered with the study drug or during the study period up through the TOC (Day +5 to +11 post-treatment) visit unless the patient failed treatment.

- Adequate compliance must have been documented for each patient with ≥ 80% of study medication taken.

- No protocol violation may have occurred during the course of therapy influencing treatment efficacy.

- The study blind could not have been broken.

2. Valid for Safety (i.e., Intent-to-Treat) Population

Supportive analyses were performed on this population, which includes all patients who received at least one dose of medication.

Reviewer's Comment: The applicant did not specify a Modified Intent-to-Treat (MITT) population, which would include all patients with a pathogen identified at baseline who received at least one dose of study drug. The Division defined and evaluated an MITT population, in addition to the applicant's valid for efficacy (Per Protocol) population. See Results section for additional information.

B. Applicant's Proposed Efficacy Analysis

The primary efficacy objective of the study is to demonstrate non-inferiority of the Cipro XR 1000 mg once daily group to the Cipro 500 mg twice daily (BID) group. A two-sided 95% confidence interval for the weighted difference between the eradication rates for each treatment group (Cipro XR minus Cipro BID) was constructed using Mantel-Haenszel weights (weighting by infection type). Non-inferiority was defined statistically as the lower limit of the two-sided 95% confidence interval for the difference between groups being less than -10%. In addition to the Mantel-Haenszel confidence interval, supportive confidence intervals were constructed using the normal approximation to the binomial distribution, with a continuity correction.

Analysis of infection type by treatment interaction for the primary efficacy variable was planned, using either the Breslow-Day test or Zelen's test. If the interaction was significant, exploratory analyses were planned to investigate the source of the interaction.

Reviewer's Comment: Although not specified by the applicant in their protocol, if an infection type by treatment interaction at the TOC visit is seen, the Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients.

For analyses performed on the valid-for-efficacy (Per Protocol) population, missing and indeterminate responses were to be excluded. For the valid-for-safety (Intent-to-Treat) population, these responses were to be included as failures.

Statistical tests also were planned for comparability of demographic data and baseline medical characteristics. Chi-square tests were planned for categorical variables, and one-way analysis of variance was planned for continuous variables.

C. Applicant's Proposed Safety Analysis

Comparisons of the incidence rates of adverse events were done in a descriptive manner. Events were to be tabulated by type (according to the COSTART glossary) and frequency for all events and for those events considered by the investigator to have a study drug relationship of possible or probable. Laboratory data were to be analyzed using descriptive statistics and identification of values outside the normal range.

XIV. Changes in the Conduct of the Study

The original protocol was amended 7 times during the study. A summary of each amendment is provided below.

Amendment 1 – March 19, 2001

The purpose of the amendment was to incorporate changes to the protocol based on suggestions from the FDA at the End of Phase II meeting. These changes included:

- Revising the number of study centers participating in the study
- Add examples of symptoms of lower urinary tract infection that may be seen with pyelonephritis
- Revising the sample size estimate based on a change in the lower limit of equivalence for the difference between treatment groups (i.e., delta) from -15 percentage points to -10 percentage points
- Clarifying the process for handling blood culture specimens
- Adding the requirement for a local lab to perform blood cultures
- Modifying the Trial Flow Chart

Amendment 2 – April 25, 2001

The purpose of the amendment was to incorporate additional changes to the protocol due to suggestions from the FDA. These revisions included:

- Modifying the language in the inclusion criteria regarding contraception use by women of childbearing potential
- Clarifying that the efficacy results would be presented descriptively by strata based on the presence or absence of pyelonephritis

Amendment 3 – July 16, 2001

The purpose of this amendment was to change the definition of Recurrence (Bacteriological outcome at the Late Follow-up Visit) from $> 10^5$ CFU/mL to $\geq 10^4$ CFU/mL before or at the +28 to +42 day post-treatment visit.

Amendment 4 – October 26, 2001

The purpose of this amendment was to remove restriction of enrollment of patients presenting with an onset of signs or symptoms of 72 hours or less prior to study entry.

Amendment 5 – December 10, 2001

The purpose of this amendment was to:

- Change the signs in the inclusion criteria for the complicated UTI patients (Stratum II) from two signs and symptoms to one sign and symptom plus an underlying complicating condition.
- Decrease the validity rate (from 75% to 50%) and the power of the study (from 90% to 85%) and increase the total number of bacteriologically valid patients enrolled (from 306 to 474). In addition, the true failure rate was reduced (17% to 15%).

Amendment 6 – April 16, 2002

The purpose of this amendment was to:

- Replace the ICD-9 Code with MedDRA code
- Clarify the classification of two or more pathogens isolated from a baseline urine culture
- Provide specific schedule for possible concomitant administration of sucralfate, divalent and trivalent cations, multivitamin preparations or antacids relative to study drug administration
- Correct the study visit window during which a systemic bacterial agent cannot be administered for a patient to be judged evaluable for efficacy analysis
- Clarify the terms “Clinical Cure” and “Clinical Failure”
- Correct the weighted difference rate
- Add INR and serum glucose to the list of safety laboratory tests
- Slightly revise the definition of an adverse event

Amendment 7 – September 12, 2002

Before the database was locked and the study blind broken the final amendment was submitted. The purpose of the amendment was to:

- Expand the Test-of-Cure visit window from 5 to 9 days to 5 to 11 days after the last dose of study drug

> *Reviewer’s Comment: The applicant expanded the TOC visit window in order to include more data in the analyses, since they noted a number of the patient visits occurring outside the protocol-specified window. This change resulted in the inclusion of 19 additional valid-for-efficacy patients in the analysis at the TOC visit. The long-term follow-up window of +28 to +42 days after the end of therapy was not changed.*

- Correct an omission (insert the words (“. . . stratified and then . . .”) in the Overall Design and Plan of Trial section of the protocol on page 21
- Correct a typographical error in the definition of “Clinical Cure” on page 40 of the protocol
- Change the definition of “Clinical Failure” at the Test-of-Cure visit and at the time study drug therapy is prematurely discontinued back to what was stated in the original protocol, which voids the change made in Amendment 6.
- Decrease the validity rate (from 50% to 39%) and decrease the total number of bacteriologically valid patients enrolled (from 474 to 404). The power of the

study was not changed (85%). In addition, the observed failure rate was reduced (15% to 12%).

XV. Clinical Reviewer's Data Validation Methods

Validation of the efficacy data was performed by obtaining the patient Case Report Forms for 10% of all randomized patients (N=113). The patients were randomly selected (blinded to treatment) and independently reviewed.

Reviewer's Comment: The reviewer determined that the trial was conducted in accordance with the draft Guidance document and as delineated in the original protocol. The reviewer's assessment of evaluability is the same as the applicant's for all patients in this sample.

RESULTS FOR STUDY 100275

I. Investigators

One thousand forty-two (1042) patients were enrolled at 100 investigative centers. Of the 1042 patients, 521 were assigned randomly to treatment with Cipro XR 1000 mg QD and 521 were assigned randomly to Cipro 500 mg BID.

The number of randomized patients by treatment group and investigator site can be found in Table 2 in Appendix 2. The mean number of patients enrolled is 10 per site (range 1-57). Dr. Siami's site has the largest number of randomized patients at 5.5% (57/1042) of the total population. The other top enrolling sites were Dr. Young (N=47), Dr. Tomera (N=42), Dr. O'Mahony (N=42), and Dr. Wachs (N=39).

II. Patient Accountability

The reasons for premature discontinuation from the study drug are shown in Table 3. There are 119 patients in the Cipro XR group and 91 patients in the Cipro BID group who did not complete the study as planned. There is a higher rate of premature discontinuation in the Cipro XR group than in the Cipro BID group, which is due primarily to protocol violations and adverse events. The most common protocol violations resulting in discontinuation are lack of causative organisms (i.e., no pre-therapy pathogen recovered, organism recovered at $<10^5$ CFU/mL, or no urine culture specimen obtained) and presence of a resistant organism.

TABLE 3
Reasons for Premature Discontinuation of Study Drug

	Cipro XR (N=521)	Cipro BID (N=521)
Any reason (*P* value=0.03)	119 (23%)	91 (17%)
Adverse event	28 (5%)	20 (4%)
Patient non-compliance	8 (2%)	7 (1%)
Consent withdrawn	9 (2%)	11 (2%)
Insufficient therapeutic effect	7 (1%)	4 (<1%)
Patient lost to follow-up	17 (3%)	13 (2%)
Death	2* (<1%)	0 (0%)
Protocol violation	48 (9%)	36 (7%)

* An additional 2 deaths were reported (one in Cipro XR at Day +35 and one in Cipro BID at Day +97 following study drug therapy).

The distribution of patients valid for the safety and efficacy analyses and the reasons for exclusion are shown in Table 4. The proportion of patients valid for efficacy (Per Protocol) is slightly smaller in the Cipro XR group (39.5%) compared to the Cipro BID group (44%).

The Cipro XR group has a slightly lower rate (34%) of patients who have no causative organism (i.e., no pathogen recovered, organism recovered at $<10^5$ CFU/mL, or no urine culture was done) compared to the Cipro BID group (37%). The Cipro XR group also has a higher rate (15%) of patients who have no valid TOC

urine culture result (i.e., urine culture specimen was not obtained at the TOC visit, or urine culture specimen was obtained outside the TOC visit window) as compared to the Cipro BID group (9%). The proportion of invalid patients due to the reasons organism resistant to study drug and exclusion/inclusion criteria violation also is slightly higher in the Cipro XR group (4% and 2%, respectively) as compared to the Cipro BID group (3% and 1%, respectively).

Reviewer's Comment: The applicant's category "Protocol violation" includes 16 catheterized patients, all having two or more causative organisms recovered from the pre-therapy urine culture specimen without the same organism isolated from blood. Six other catheterized patients have reasons that could have classified them as a "protocol violation", but instead were classified otherwise by the applicant (five as "organism resistant to study drug" and one as "exclusion/inclusion criteria violation").

Reviewer's Comment: Table 4 is modified from the applicant's submission by the reviewer for clarity.

TABLE 4
Patients Validity and Reasons for Exclusion from Analyses
All Randomized Patients (N=1042)

	Cipro XR (N=521)	Cipro BID (N=521)
All Randomized Patients	**521**	**521**
Patients Valid for Safety (i.e., Intent to Treat)	**517 (99.2%)**	**518 (99.4%)**
Patients Valid for Efficacy (i.e., Per Protocol)	**206 (39.5%)**	**229 (44.0%)**
Excluded from Safety (Intent to Treat) Analysis	**4 (0.8%)**	**3 (0.6%)**
Patient never received any study medication	4 (0.8%)	3 (0.6%)
Excluded from Efficacy (Per Protocol) Analysis	**315 (60.5%)**	**292 (56.0%)**
No causative organism isolated pre-treatment[a]	175 (33.6%)	194 (37.2%)
Inadequate duration of treatment	1 (0.2%)	4 (0.8%)
Concomitant antimicrobial therapy	1 (0.2%)	1 (0.2%)
Organism resistant to study drug	21 (4.0%)	15 (2.9%)
Noncompliance with study medication	5 (1.0%)	5 (1.0%)
Exclusion/Inclusion criteria violation	21 (4.0%)	16 (3.1%)
Insufficient required clinical symptoms for inclusion	11 (2.1%)	9 (1.7%)
Lack of underlying condition	5 (1.0%)	2 (0.4%)
Liver disease or liver impairment	2 (0.4%)	1 (0.2%)
Pre-therapy antibiotics taken	3 (0.6%)	1 (0.2%)
Prohibited concomitant medication	0 (0%)	3 (0.6%)
Patient never received any study medication	4 (0.8%)	3[b] (0.6%)
Post-therapy antibiotics taken	2 (0.4%)	2 (0.4%)
Protocol violation	9 (1.7%)	7 (1.3%)
No valid TOC urine culture[c]	76 (14.6%)	45 (8.6%)

[a] no pre-therapy pathogen recovered, organism $<10^5$ CFU/mL, or no urine culture specimen obtained
[b] antacids or multivitamin preparations taken in violation of the protocol within 6 hours before or less than 2 hours after the dose of study drug
[c] urine culture specimen was not obtained at the TOC visit, or urine culture specimen was obtained outside the TOC visit window (5 to 11 days post-treatment)

Reviewer's Comment: Table 4A presents the number of patients valid for analyses in each of the Division's three populations, including the MITT.

TABLE 4A
Patients Valid for Analyses
All Randomized Patients (N=1042)

	Cipro XR	***Cipro BID***
All Randomized Patients	*521*	*521*
*Patients Valid for Safety (i.e., Intent to Treat)**	*517 (99.2%)*	*518 (99.4%)*
*Patients Valid for MITT (i.e., modified Intent to Treat)***	*342 (65.6%)*	*324 (62.2%)*
*Patients Valid for Efficacy (i.e., Per Protocol)****	*206 (39.5%)*	*229 (44.0%)*

** Four (4) patients in the Cipro XR group and 3 patients in the Cipro BID were excluded because they never received any study medication.*
*** 175 patients in the Cipro XR group and 194 patients in the Cipro BID were excluded due to no pathogen identified at baseline.*
****Three hundred and fifteen (315) patients in the Cipro XR group and 292 patients in the Cipro BID group were excluded for various reasons (see Table 4 above).*

Reviewer's Comment: On June 18, 2003 the applicant was asked to provide additional information regarding the reasons patients were classified as "No Valid TOC urine culture" (see Table 4) by providing a tabulation of the number of patients with each specific cause for not conducting the TOC urine culture (e.g., discontinuation due to adverse event, death, lab error, etc.).

On June 27, 2003 the applicant submitted Table 4B shown below. The reviewer investigated all individual patients excluded by the applicant in the PP population due to "protocol violations" within the "No TOC urine culture" category and determined that patients were not always categorized by the major reason for exclusion. For example, a patient in the category "No valid TOC urine culture" may have been excluded due to a ciprofloxacin resistant pathogen, and yet there is also an exclusion category called "Organism Resistant to Study Drug" (see Table 4).

As a result, the reviewer sent a request to the applicant in a fax on July 17, 2003, asking the applicant to reclassify patients based upon the root cause for exclusion from the PP population. The applicant was asked to avoid categories of "protocol violation" and "no valid TOC urine culture", as they are too non-specific.

On July 29, 2003 the applicant submitted the revised data. Upon review, the reviewer noted the reasons for exclusion of individual patients (provided by the applicant) within the new exclusion categories of "no TOC visit", "lost to follow-up", and "TOC outside the 5-11 day window", did not always match the title of the exclusion category. For example, patients 50012 and 15004 were classified as "no TOC visit" and yet the comments from the patient's CRFs indicated that these patients had ciprofloxacin resistant organisms.

The reviewer accepts the applicant's revised classification of reasons for exclusion of patients from the PP population, despite the inconsistencies noted above because they are not believed to have a significant impact on the overall results. Table 4 was

recreated by the reviewer, using the revised data submitted by the applicant on July 29, 2003, and the results can be seen in Table 5.

TABLE 4B
Patients Invalid in the Per Protocol (or Valid for Efficacy) Population
Due to No TOC Urine Culture

	Cipro XR	Cipro BID
Invalid due to No TOC Urine Culture	**76 (15%)**	**45 (9%)**
Premature Discontinuation due to: Any Reason	**44 (8%)**	**25 (5%)**
Adverse Event	14	6
Noncompliance with Drug	0	1
Consent Withdrawn	3	5
Insufficient Therapeutic Effect	1	1
Lost to Follow-up	8	4
Death	2	0
Protocol Violation	16	8
Completed Therapy, but No TOC Urine Culture	**11 (2%)**	**7 (1%)**
TOC Culture Outside 5-11 Day Post-Treatment Window	**21 (4%)**	**12 (2%)**
Before Day 5	12	4
After Day 11	9	8
Lost to Follow-up, no discontinuation reason given	**0**	**1**

TABLE 5
Patients Validity and Reasons for Exclusion from Analyses
All Randomized Patients (N=1042)
Revised by Applicant

	Cipro XR (N=521)	Cipro BID (N=521)
All Randomized Patients	**521**	**521**
Patients Valid for Safety (i.e., Intent to Treat)	**517 (99.2%)**	**518 (99.4%)**
Patients Valid for Efficacy (i.e., Per Protocol)	**206 (39.5%)**	**229 (44.0%)**
Excluded from Safety (Intent to Treat) Analysis	**4 (0.8%)**	**3 (0.6%)**
Patient never received any study medication	4 (0.8%)	3 (0.6%)
Excluded from Efficacy (Per Protocol) Analysis	**315 (60.5%)**	**292 (56.0%)**
No causative organism (isolated pre-treatment)	175 (33.6%)	194 (37.2%)
Concomitant or post-therapy antimicrobial	3 (0.6%)	3 (0.6%)
Organism resistant to ciprofloxacin	31 (6.0%)	18 (3.4%)
Noncompliance with study medication	5 (1.0%)	6 (1.2%)
Inclusion criteria violation	21 (4.0%)	16 (3.1%)
Patient never received any study medication	4 (0.8%)	3 (0.6%)
More than two causative organisms identified for catheterized patients	9 (1.7%)	7 (1.3%)
Premature discontinuation due to adverse event(s)	15 (2.9%)	9 (1.7%)
Lost to follow-up	8 (1.5%)	4 (0.8%)
Death	2 (0.4%)	0
Consent withdrawn	3 (0.6%)	5 (1.0%)
Insufficient therapeutic effect	1 (0.2%)	1 (0.2%)
Pre-therapy lab value violation	6 (1.2%)	6 (1.2%)
TOC culture outside 5-11 day window	21 (4.0%)	12 (2.3%)
No TOC visit	11 (2.1%)	8 (1.5%)

Reviewer's Comment: Exclusions from the PP population are greater in the Cipro XR group compared to the Cipro BID group and a differential rate in exclusion may bias the results of any analysis using this population. Therefore, the Division analyzed the results for the Modified Intent-to-Treat (MITT) population, in addition to the PP population. In the MITT population (all patients with a pathogen identified at baseline), missing and indeterminate results are included as failures.

III. Patient Groups

A. Demographic Characteristics

Demographic and other important baseline characteristics for the population of patients valid for efficacy are presented in Table 6.

The mean age (± standard deviation) of patients valid for efficacy is 60.1 (± 19.1) years in the Cipro XR treatment group and 61.2 (± 19.4) years in the Cipro BID group. The minimum age in both treatment groups is 18 years, and the maximum age is 96 years and 92 years in the Cipro XR and Cipro BID groups, respectively. There are more female than male patients in both treatment groups (57% in the Cipro XR group and 55% in the Cipro BID group). Most of the patients are Caucasian (82% in the Cipro XR group and 77% in the Cipro BID group. Among patients who are not Caucasian, most are categorized as Black or Hispanic (18% and 22% in the two treatment groups, respectively). Less than 1% of patients in each treatment group are Asian.

There are no statistically significant differences in demographic or baseline characteristics between treatment groups, and in general, the distribution of demographic variables is similar in the two groups. When demographic and baseline characteristics are examined by diagnosis group, the characteristics are also similar. These results are consistent with those observed for the population of patients valid for safety (data not shown).

TABLE 6
Key Demographic and Infection Characteristics
Patients Valid for Efficacy

	Cipro XR (N=206)	Cipro BID (N=229)
Age at enrollment (years), mean	60.1	61.2
Sex, % female	57%	55%
Race, % Caucasian	82%	77%
Weight at enrollment (kg), mean	75.8	77.9
Body mass index, mean	26.6	27.4
Health status before study entry, %		
Excellent	30%	19%
Good	51%	59%
Fair	18%	21%
Poor	<1%	<1%
Duration of infection (days) mean ± SD, range	4.7 ± 9.1 (1 to 121)	4.4 ± 4.7 (1 to 34)
Infection type, % cUTI	81%	77%
Number of underlying conditions for cUTI, %[a]		
1	72%	79%
2	25%	19%
>2	3%	2%

[a] Denominator is number of patients with cUTI (n=166 for Cipro XR; n=177 for Cipro BID)

Reviewer's Comment: In order to characterize the demographics of cUTI compared to AUP patients, the reviewer analyzed the age and gender of patients in both subgroups. The number of underlying conditions could not be compared between the groups, since the presence of underlying conditions was not required for AUP patients. As shown in Table 6A, patients with AUP are more likely to be young and female, compared to the cUTI patients.

TABLE 6A
Demographic Characteristics for AUP and cUTI Patients
Patients Valid for Efficacy

	AUP Patients		*cUTI Patients*	
	Cipro XR N=40	*Cipro BID N=52*	*Cipro XR N=166*	*Cipro BID N=177*
Mean age at enrollment	*41 years*	*40 years*	*64 years*	*67 years*
Number Female	*33*	*43*	*85*	*84*
Number Male	*7*	*9*	*81*	*93*

B. Bacteriology

Overall, patients with at least one causative organism comprised 342 valid for efficacy patients in the Cipro XR group (66.1%) and 324 (62.5%) patients in the Cipro BID group. The most common organisms (≥ 10 in either treatment arm)

isolated from the urine are summarized by diagnosis and treatment group in the valid for efficacy population in Table 7. Some patients have more than one organism isolated at enrollment. The Cipro XR group has slightly fewer valid for efficacy patients with causative organisms in the urine regardless of infection type; however, the numbers of patients with each common causative organism are similar in the two treatment groups.

TABLE 7
Most Common (≥10 organisms per Treatment Group) Causative Organisms in Urine at Enrollment
Patients Valid for Efficacy [a]

	Cipro XR	Cipro BID
AUP patients with at least 1 organism	40	52
Escherichia coli	36	41
cUTI patients with at least 1 organism	166	177
Escherichia coli	94	92
Klebsiella pneumoniae	23	23
Enterococcus faecalis	18	21
Proteus mirabilis	12	11

[a] A patient could have more than one organism

Escherichia coli was isolated from the pre-treatment (enrollment) blood culture specimen of 9 AUP patients (5 in the Cipro XR group and 4 in the Cipro BID group). E. *coli* was the only causative organism recovered from the blood of patients with cUTI (one in each treatment group).

These results are consistent with those observed for the population of patients valid for safety. Patients with at least one causative organism comprised 327 valid for safety patients in the Cipro XR group (63%) and 315 (61%) patients in the Cipro BID group. Among patients who had a causative organism in the urine, 207 are non-evaluable in the efficacy analysis due primarily to no TOC culture (n=121), exclusion/inclusion criteria violation (n=35), or isolation of ciprofloxacin-resistant organisms at pre-therapy (n=31).

Eight (8) patients in the valid for safety population received antimicrobial agents before the start of study drug therapy (6 in the Cipro XR group and 2 in Cipro BID group). Five different antimicrobial drugs were used (ciprofloxacin [ophthalmic and systemic], ofloxacin, methenamine, nitrofurantoin, and metronidazole).

C. Concomitant Medications

The incidence rate of concomitant medication use (i.e., medications started after randomization) in the valid for safety population is 23% in the Cipro XR group and 24% in the Cipro BID group. The most commonly used treatment-emergent medications are in the nervous system class (12% in the Cipro XR group and 13% in the Cipro BID group) for reasons including flank pain, headache, back pain, fever, anesthesia, etc. The rates of use of concomitant medications by medication class are consistent in the two treatment groups.

In the valid for safety population, 38 patients in the Cipro XR group and 16 patients in the Cipro BID group received concomitant antimicrobials. Antimicrobial agents used more frequently include trimethoprim/ sulfamethoxazole (4 and 0 patients in the Cipro XR and Cipro BID groups, respectively), ceftriaxone (3 and 2, respectively), and nitrofurantion (6 and 2, respectively).

D. Signs and Symptoms of Disease

All valid for efficacy patients with AUP reported the presence of chills, flank pain, and fever as specified in the protocol. In 77% of patients, flank pain is rated as moderate or severe. The most common additional signs and symptoms in valid patients with pyelonephritis are backache (92%), urgency (91%), frequency (90%), and malaise (85%). Vomiting (33%) and hematuria (46%) are the only symptoms present in less than 80% of the AUP patients.

Frequency is the most common symptom in the complicated UTI patients (87% of valid cUTI patients had this symptom). The two treatment groups are well balanced with respect to the distribution of signs/symptoms and their severity in both diagnosis groups (i.e., AUP and cUTI).

E. Underlying Conditions (cUTI group)

The percentage of valid for efficacy patients with cUTI who have more than one valid underlying condition is higher in the Cipro XR (28%) than the Cipro BID (21%) group as shown in Table 6 above. Table 8 presents a summary of the distribution of underlying conditions at study entry. The underlying conditions reported include the five specified in the protocol (i.e., 100 mL residual urine after voiding; urinary retention due to benign prostatic hypertrophy; indwelling urinary catheter; neurogenic bladder; and obstructive uropathy due to nephrolithiasis, tumor, or fibrosis) plus additional underlying conditions (i.e., bladder cancer, other anatomical abnormalities, obstructive uropathy due to other etiology, and cystocele or cystourethrocele).

Reviewer's Comment: According to the applicant's statistical plan, patients with indwelling catheters that grew two or more pathogens from the baseline urine culture were to be considered unevaluable in the efficacy population, unless the same pathogen was also isolated from a simultaneously obtained blood culture specimen. If the same pathogen grew in the urine at $\geq 10^5$ CFU/mL and was isolated from the blood, then the patient would be considered to be evaluable. None of the 21 patients with indwelling catheters grew two or more pathogens from the baseline blood culture. There are 20 patients (9 Cipro XR and 11 Cipro BID patients) without indwelling catheters in the valid for efficacy population who grew multiple pathogens.

The combination of underlying conditions is shown in Table 8. Patients are reported according to one underlying condition alone or a specific underlying condition plus other underlying conditions. The two treatment groups are similar with respect to the distribution of type of underlying condition(s).

Reviewer's Comment: Table 8 is modified from the applicant's submission by the reviewer for clarity.

TABLE 8
Underlying Conditions for cUTI Patients at Study Entry
cUTI Patients Valid for Efficacy

	Number (%)	
	Cipro XR (N=166)	Cipro BID (N=177)
100 mL Residual Urine after Voiding	64 (39)	71 (40)
alone	*37 (22)*	*41 (23)*
plus other condition	*27 (16)*	*30 (17)*
Benign Prostatic Hypertrophy with Urinary Retention	35 (21)	34 (19)
alone	*12 (7)*	*20 (11)*
plus other condition	*23 (14)*	*14 (8)*
Indwelling Urinary Catheter	12 (7)	9 (5)
alone	*2 (1)*	*2 (1)*
plus other condition	*10 (6)*	*7 (4)*
Neurogenic Bladder	51 (31)	61 (34)
alone	*34 (20)*	*45 (25)*
plus other condition	*17 (10)*	*16 (9)*
Obstructive Uropathy due to Nephrolithiasis, Tumor, or Fibrosis	49 (40)	38 (21)
alone	*34 (20)*	*28 (16)*
plus other condition	*15 (9)*	*10 (6)*
Bladder Cancer	1 (1)	0 (0)
alone	*0 (0)*	
plus other condition	*1 (1)*	
Other Anatomical Abnormalities/Obstructive Uropathy Due to Other Etiology	4 (2)	5 (3)
alone	*0 (0)*	*4 (2)*
plus other condition	*4 (2)*	*1 (1)*
Cystocele/Cystourethorocele	5 (3)	1 (1)
alone	*0 (0)*	*0 (0)*
plus other condition	*5 (3)*	*1 (1)*

F. Adjunct Therapeutics/Procedures

In the valid for safety population, 51 (10%) patients in the Cipro XR group and 37 (7%) patients in the Cipro BID group required a therapeutic adjunct or diagnostic/surgical procedure. The most frequently identified therapeutic adjuncts are the administration of intravenous fluids (17 Cipro XR patients vs. 14 Cipro BID patients) and the use of a urinary catheter (e.g., indwelling [16 Cipro XR patients vs. 10 Cipro BID patients] and intermittent [10 Cipro XR patients vs. 6 Cipro BID patients]). The proportion of patients using each adjunct is similar between groups.

IV. Compliance Results

The number of tablets taken is summarized in Table 9 for all patients valid for efficacy and safety. All of these patients received treatment over a course of 5 to 15 days, with a mean (± SD) of 12 ± 3 days in both groups.

Reviewer's Comment: Table 9 is modified from the applicant's submission by the reviewer for clarity.

TABLE 9
Medication Compliance by Number of Tablets Taken

Number of Tablets Missing (Presumed Taken)	Number of Patients (% of Total Population)			
	Valid for Efficacy		Valid for Safety	
	Cipro XR (N=206)	Cipro BID (N=229)	Cipro XR (N=517)	Cipro BID (N=518)
< 6	0 (0)	0 (0)	27 (5)	14 (3)
> 6 to 18	0 (0)	4 (2)	48 (9)	41 (8)
> 18 to 30	81 (39)	84 (37)	171 (33)	170 (33)
> 30 to 42	119 (58)	137 (60)	248 (48)	273 (53)
Missing Data	6 (3)	4 (2)	23 (4)	20 (4)

Of note, during the conduct of the study, a short-fill in Bottle #2 was discovered for patient numbers 601 through 900. The short-fill resulted in 23 placebo tablets placed in Bottle #2 instead of 28 placebo tablets. On October 31, 2001, the applicant became aware of the situation and on November 1, 2001 notified all sites and instructed them not to dispense medication bottles with numbers 601 through 900. Sixteen patients were affected by the short-fill and all were in the Cipro XR group. Of these, 8 are considered valid for efficacy and safety and all 8 received at least 7 days of study medication. One of the 8 patients (98001) had 11 days of therapy and had a persistence at the TOC. The remaining 8 patients are valid for safety only.

V. Efficacy Results for the Valid for Efficacy Population – Bacteriologic Response

A. Eradication at the TOC Visit

The bacteriological eradication rate at the TOC visit in patients valid for efficacy, the primary efficacy variable, is shown in Table 10. Overall eradication in cUTI and AUP patients combined is 88.8% in the Cipro XR group and 85.2% in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (–2.4%, 10.3%) is above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

Reviewer's Comment: In addition to the Mantel-Haenszel confidence interval, the applicant calculated supportive confidence intervals using the normal approximation to the binomial distribution, with a continuity correction. For the difference in bacteriological eradication rates at the TOC visit in patients valid for efficacy, the 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-3.1%, 10.4%).

TABLE 10
Number of Patients (%) with Bacteriological Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Efficacy

	Cipro XR	**Cipro BID**
All Patients	(N=206)	(N=229)
Eradication	183 (88.8%)	195 (85.2%)
Persistence	10 (4.9%)	17 (7.4%)
Superinfection	5 (2.4%)	3 (1.3%)
New infection	8 (3.9%)	14 (6.1%)
Eradication Rate[a]	**183/206 (88.8%)**	**195/229 (85.2%)**
AUP Patients	(n=40)	(n=52)
Eradication	35 (87.5%)	51 (98.1%)
Persistence	2 (5.0%)	1 (1.9%)
New infection	3 (7.5%)	0
cUTI Patients	(n=166)	(n=177)
Eradication	148 (89.2%)	144 (81.4%)
Persistence	8 (4.8%)	16 (9.0%)
Superinfection	5 (3.0%)	3 (1.7%)
New infection	5 (3.0%)	14 (7.9%)

[a] Eradication rate for all patients (cUTI plus AUP); 95% Confidence Interval: (-2.4%, 10.3%)

The *P* value from the Breslow-Day test for treatment-by-infection interaction is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients.

Reviewer's Comment: Since there is a treatment-by-infection interaction, the Division dos not consider it appropriate to pool results for patients with AUP and cUTI. Therefore the clinical and statistical reviewers evaluated AUP and cUTI patients separately.

The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%) [corresponding 97.5% confidence interval of the difference (-34.8%, 6.2%)]. In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the Cipro BID group (81.4%) [corresponding 97.5% confidence interval of the difference* (-0.7, 16.3%)].*

**When calculating the results of each stratum alone an adjustment must be made for multiple comparisons (i.e., use of 97.5% confidence intervals for the differences between Cipro XR and Cipro BID within the AUP and cUTI subgroups).*

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10%, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above -10% (and almost above

zero), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority).

Additional analyses were performed in an attempt to assess how Cipro XR compares to Cipro BID with respect to persistence of the baseline pathogen and subsequent clinical response. See the following sections on AUP and cUTI patients.

1. AUP Patients

When comparing all patients with a diagnosis of AUP, the two treatment arms are well balanced with respect to demographics, baseline characteristics, and severity of signs and symptoms at study entry (data not shown).

Of the 40 patients with AUP treated with Cipro XR, 35 were eradicated (32 *E. coli*, 1 *P. aeruginosa*, 2 *K. pneumoniae*), 2 had persistence (1 *E. coli* and 1 *E. faecalis*), and 3 developed new infections with *E. facecalis* (2 with *E. coli* as baseline pathogen and one with *S. aprophyticus*).

Of the 52 patients with AUP treated with Cipro BID, 51 were eradicated (40 *E. coli*, 2 *P. mirabilis*, 3 *E. faecalis*, 2 *K. pneumoniae*, 1 each with *C. koseri*, S. *aureus*, S. *saprophyticus*, W. *virosa*; and one with *E. coli* and *P. mirablis*, one with *E. coli* and *E. faecalis*, and one *E. faecalis* and *C. koseri*). One patient had persistence of *E. faecalis*.

In the AUP patients treated with Cipro XR, three developed a new infection as compared to none in the Cipro BID group, as shown in Table 11. A short narrative of each patient's clinical course follows the table.

Two of the 3 patients had *E. coli* isolated as the causative organism at the pre-therapy visit and developed *E. faecalis* in a quantity of $\geq 10^5$ CFU/mL at the TOC visit. Neither had any clinical signs or symptoms of infection at the TOC or late follow-up visits, and no alternative antibiotics were deemed necessary by the investigator.

Reviewer's Comment: The emergence of Enterococcus species as a new pathogen at the TOC visit in three patients in the Cipro XR arm is notable. In order to better understand the effect of ciprofloxacin on Enterococcus, the reviewer identified all AUP patients with Enterococcus species isolated at baseline or the TOC visit. There are 10 patients with AUP (4 in the Cipro XR group and 6 in the Cipro BID group) that had an Enterococcus species isolated at baseline or the TOC visit. Of the 4 Cipro XR patients, three had new infections with Enterococcus sp. at the TOC visit (see Table 10 above) and the fourth had persistence of Enterococcus faecalis from baseline (patient 0209039). No patient in the Cipro XR arm had Enterococcus isolated at baseline. Of the 6 Cipro BID patients, five had Enterococcus faecalis isolated at baseline and were eradicated of at the TOC visit (patients 148024, 029042, 082040, 148019, 148027) and the sixth had persistence of Enterococcus faecalis from baseline (patient 013017). No patient in the Cipro BID arm developed a new infection due to Enterococcus at the TOC visit.

Reviewer's Comment: Table 11 has been modified from the applicant's table by the reviewer for clarity.

TABLE 11
Cipro XR Patients with AUP who Experienced a New Infection at the TOC Visit

Patient No.	Age (yr)/Sex	Duration of Treatment (d)	Urine Pathogen(s)	MIC (μg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
62019	21/F	10	*E. coli* (pre-therapy)	0.015	Eradication (Continued eradication)	Cure (Continued cure)	No
			E. faecalis (TOC)	1.00	New Infection (Eradication)		
82039	19/F	8	*E. coli* (pre-therapy)	0.015	Eradication (Continued eradication)	Cure (Continued cure)	No
			E. faecalis (TOC)	0.5	New Infection (Eradication)		
			E. faecium (TOC)	16	New Infection (Eradication)		
148023	18/F	11	*S. saprophyticus* [a] (pre-therapy)	0.120	Eradication (Indeterminate)	Cure (Cure [b])	Yes [c]
			E. faecalis (TOC)	1.00	New Infection (Indeterminate)		

[a] Pre-therapy urine culture also contained 65,000 CFU/mL of *E. coli* (MIC 0.015 μg/mL)
[b] Post-alternative therapy visit
[c] Ciprofloxacin 500 mg BID for 7 days following the completion of study drug

Patient Narratives

Patient 62019 is a 21-year-old female with a medical history significant for a urinary tract infection in 1999. She was not receiving any concomitant medications. The patient presented with 4 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mild/moderate signs
and symptoms except for severe dysuria and back pain. Her temperature at study entry was 38.3° C (orally), and the white blood cell (WBC) count was 9.7 x 10^9 /L. Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro XR 1000 mg QD, which she received for 10 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to 6.8 x 10^9 /L. A repeat urine culture result at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* was identified in a quantity of $\geq 10^5$ CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient remained afebrile and her response was evaluated as continued clinical cure. Urine culture results revealed continued eradication of *E. coli* and absence of *E. faecali*s.

Patient 82039 is a 19-year-old female with no significant medical history. Concomitant medications included acetaminophen and an oral contraceptive agent. The patient presented with 3 days of signs and symptoms of pyelonephritis, a temperature of 38.3° C (orally), and a WBC count of 11.6 x 10^9 /L. Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro XR 1000 mg QD, which she received for 8 days. At the TOC visit, the patient's rsponse was evaluated as clinical cure (no remaining signs or symptoms of infection). The WBC count had decreased to 6.4 x 10^9 /L. A repeat urine culture result obtained at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* and *E. faecium* both were identified in a quantity

$\geq 10^5$ CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient's response was assessed as continued clinical cure. Urine culture results at follow-up revealed continued eradication of *E. coli* and absence of both *Enterococcus* species.

Patient 148023 is an 18-year-old female with no significant medical history, and she was not receiving any concomitant medications. The patient presented with 2 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mild/moderate signs and symptoms, a temperature of 38.8° C (orally), and a WBC count of 9.7 x 10^9 /L. Her pretherapy urine culture result was positive for *S. saprophyticu*s, and she was assigned randomly to treatment with Cipro XR 1000 mg QD, which she received for 11 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to 5.5 x 10^9 /L. A repeat urine culture result at the TOC visit was negative for *S. saprophyticus* (eradication); however, *E. faecalis* was identified in a quantity of $\geq 10^5$ CFU/mL (new infection). Alternative antibiotic therapy was prescribed (ciprofloxacin 500 mg BID for 7 days) 18 days following the completion of study drug therapy. At the post-alternative therapy visit the patient's clinical response was evaluated as clinical cure; there was no follow-up bacteriological evaluation.

2. cUTI Patients

As previously mentioned, among patients with cUTI, the bacteriologic eradication rates at the TOC visit are higher in the Cipro XR group (148/166, 89.2%) compared to the Cipro BID group (144/177, 81.4%). The 97.5% confidence interval of the difference is [-0.7, 16.3%].

Of the 166 patients with cUTI treated with Cipro XR, 148 were eradicated, 8 have persistence with the following organisms: *E. coli* (3), *S. aureus* (2), and *K. pneumoniae*, *P. mirabilis*, and *C. freundii* (one each). Five patients developed superinfections with *S. aureus* (3) and *P. aeruginosa* (2) and five developed new infections with *E. faecalis* (3), and *S. aureus* and *P. stuartii* (one each).

Of the 177 patients with cUTI treated with Cipro BID, 144 were eradicated, 16 have persistence with the following organisms: *E. faecalis* (7), *K. pneumoniae* (4), *E. coli* (2), and *S. aureus*, *K. oxytoca*, and 1 *C. koseri* (one each). Three patients developed superinfections (one each of *E. faecalis*, *K. pneumoniae*, and *A. faecalis*) and fourteen developed new infections (*E. faecalis* (6), *S. aureus* (4), *E. coli*, *P. mirabilis*, *A. calcoaceticus*, *C. freundii*, and *Enterococcus* sp. (one each).

The number of patients with persistent organisms and new infections is disproportionately lower in the Cipro XR group (8 and 5, respectively) compared to the Cipro BID group (16 and 14, respectively). The organisms persisting in each treatment group are as shown in Table 12.

Reviewer's Comment: Table 12 was created by the reviewer.

TABLE 12
Organisms Persisting at TOC (+5 to +11 Days) in cUTI Patients
Patients Valid for Efficacy

	Cipro XR	Cipro BID
E. faecalis	0	7
E. coli	3	2
K. pneumoniae	1	4
S. aureus	2	1
P. mirabilis	1	0
C. freundii	1	0
K. oxytoca	0	1
C. koseri	0	1

Organisms causing new infections, or superinfections, will be discussed subsequently.

3. By Organism

The most commonly isolated organisms (≥ 10 in either treatment group) recovered from the urinary tract at the TOC visit are shown in Table 13. The eradication rates are high and similar between the groups, with the exception of *E. faecalis* in cUTI patients in the Cipro BID group.

TABLE 13
Bacteriological Eradication* at TOC Visit (+5 to +11 Days)
For the Most Common Organisms (≥ 10 in Either Treatment Group)
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	**Cipro BID**
AUP Patients		
Escherichia coli	35/36 (97%)	41/41 (100%)
cUTI Patients		
Escherichia coli	91/94 (97%)	90/92 (98%)
Klebsiella pneumoniae	20/21 (95%)	19/23 (83%)
Enterococcus faecalis	17/17 (100%)	14/21 (67%)
Proteus mirabilis	11/12 (92%)	10/10 (100%)

* n/N = patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

The minimum inhibitory concentrations at which 90% of organisms are inhibited (MIC_{90}) for the most common causative pathogens in Table 13 above are as follows: *E. coli* (0.06 µg/mL); *K. pneumoniae* (0.5 µg/mL); *E. faecalis* (2.0 µg/mL); and *P. mirabilis* (2.0 µg/mL).

Reviewer's Comment: Additional tables showing by-organism results from the Microbiologist's review can be found in Appendix 2:

Table 14 shows the microbiological results by pathogen at the TOC visit. The eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against Enterococcus faecalis than did Cipro BID. Eradication rates for E. coli, by far the most common organism, were high for both treatment groups. There were very few isolates of Enterobacter aerogenes or Pseudomonas aeruginosa.

Tables 15 and 16 show the bacteriological response for AUP and cUTI patients, respectively, by MIC value of the organism. Persistence was not associated with elevated MICs for any organism.

Tables 17 and 18 show the patients valid for efficacy that had bacteriologic persistence or were clinical failures at the TOC and follow-up visits. More bacteriologic persistence and clinical failures were seen in the Cipro BID group (n = 26) compared with the Cipro XR group (n = 15).

Table 19 shows isolates with an MIC post-therapy that was more than one dilution greater than the pre-therapy MIC. Of 65 isolates from either the Cipro XR or Cipro BID groups, eleven isolates had elevated MICs at the TOC visit. The six isolates that were in the Cipro XR group included Escherichia coli (n = 4), Klebsiella pneumoniae (n = 1), and Staphylococcus aureus (n = 1). The MICs of two isolates of Escherichia coli increased to 16 µg/mL; however, the organisms were eradicated at the TOC visit, but recurred at the follow-up visit. The MIC of one isolate of E. coli increased from 0.015 to 0.12 µg/mL and was not eradicated and the MIC of the other isolate, which recurred at the follow-up visit, increased from 0.03 to 0.5 µg/mL. The MIC of the isolate of K. pneumoniae increased from 0.06 to 0.5 µg/mL, while the MIC of the isolate of S. aureus increased from 2 to 16 µg/mL. Neither organism was eradicated. Similar results were seen in the Cipro BID group.

a) AUP Patients

All causative pathogens and the outcome in AUP patients in the Cipro XR and Cipro BID groups are shown in Tables 20 and 21 respectively.

Reviewer's Comment: Tables 20 and 21 were created by the reviewer.

TABLE 20
Bacteriological Eradication at TOC Visit (+5 to +11 Days)
AUP Patients treated with Cipro XR
Patients Valid for Efficacy (N=40) [a]

Urine Pathogens at Baseline	Eradication	New Infection	Persistence	Bacteriologic Eradication*
E. coli (N=36) [a]	33	2 (*E. faecalis*)	1	35/36 (97.2%)
E. faecalis (N=1)	--	--	1	0/1
K. pneumoniae (N=2) [a]	2	--	--	2/2 (100%)
P. aeruginosa (N=1)	1	--	--	1/1 (100%)
S. saprophyticus (N=1)	--	1 (*E. faecalis*)	--	1/1 (100%)

[a] One patient had *E. coli* and *K. pneumonia* isolated at baseline (both were eradicated)
* n/N patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

TABLE 21
Bacteriological Eradication* at TOC Visit (+5 to +11 Days)
AUP Patients treated with Cipro BID
Patients Valid for Efficacy (N=52) [a, b, c]

Urine Pathogens at Baseline	Eradication	New Infection	Persistence	Bacteriologic Eradication*
E. coli (N=41) [a, b]	41	--	--	41/41 (100%)
P. mirabilis (N=3) [a]	3	--	--	3/3 (100%)
E. faecalis (N=5) [b, c]	4	--	--	4/5 (80%)
K. pneumoniae (N=2)	2	--	--	2/2 (100%)
Citrobacter koseri (N=1) [c]	1	--	--	1/1 (100%)
S. aureus (N=1)	1	--	--	1/1 (100%)
S. saprophyticus (N=1)	1	--	--	1/1 (100%)
Weeksella virosa (N=1)	1	--	--	1/1 (100%)

* n/N patients with specified baseline pathogen eradicated/patients with specified baseline pathogen
[a] One patient had *E. coli* and *P. mirablis* isolated at baseline (both were eradicated)
[b] One patient had *E. coli* and *E. faecalis* isolated at baseline (both were eradicated)
[c] One patient had *E. faecalis* and *C. koseri* isolated at baseline (both were eradicated)

b) cUTI Patients

In addition to the 4 organisms listed in Table 13 as being the most prevalent for cUTI patients, there are also 10 infections total with *E. aerogene*s (4 in Cipro XR and 6 in Cipro BID) and 6 infections total with *P. aeruginosa* (3 in

each group). The bacteriologic eradication rates for these two additional organisms are shown in Table 22.

Reviewer's Comment: Table 22 was created by the reviewer.

TABLE 22
Bacteriological Eradication* at TOC Visit (+5 to +11 Days)
For cUTI Patients with Less Prevalent Organisms
(< 10 in Either Treatment Group)
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	**Cipro BID**
Enterobacter aerogenes	4/4 (100%)	6/6 (100%)
Pseudomonas aeruginosa	3/3 (100%)	3/3 (100%)

* n/N patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

In the entire study population there are 15 isolates of *P. aeruginosa* identified in 15 patients (1 AUP patient and 14 cUTI patients), although only 6 are obtained from cUTI patients valid for efficacy. Due to the inherent resistance and increasing rates of emerging resistance to this organism in the community, a detailed evaluation of all 15 patients with *P. aeruginosa* isolated at baseline in the Cipro XR and Cipro BID groups was performed by the reviewer and the results are shown in Tables 23 and 24, respectively.

Reviewer's Comment: Tables 23 and 24 were created by the reviewer.

TABLE 23
Cipro XR Patients with *Pseudomonas aeruginosa* as a Pathogen in Pre-Therapy Urine Culture

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Valid for Efficacy? / If no, then reason	*P. aeruginosa* MIC (µg/mL)	Bacteriological Response to *P. aeruginosa* at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
AUP Patients							
209024	74/F	14	Yes	0.03	Eradication (Continued Eradication)	Cure (Continued Cure)	No
cUTI Patients							
041019	**67/M**	**15**	**Yes**	**0.5**	**Eradication (Recurrence)**	**Cure (Continued Cure)**	**No**
042046	74/M	14	No / Resistant organism	> 16	Persistence (Persistence)	Cure (Not Reported)	No
045002	68/F	8	No / Resistant organism	> 16	Persistence and Superinfection with *E. faecalis* (Superinfection)	Not Reported (Not Reported)	Yes (amikacin and cefepime following TOC visit)
045032	**76/M**	**14**	**Yes**	**0.12**	**Eradication (Indeterminate)**	**Cure (Not Reported)**	**No**
068010	44/M	7	No / Resistant organism	16	Persistence (Persistence)	Failure (Failure)	Yes (Bactrim DS following TOC visit)
101003	87/M	3	No / No TOC urine culture; drug d/c due to dizziness as AE	4	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
142017	**79/M**	**11**	**Yes**	**0.12**	**Eradication (Continued Eradication)**	**Cure (Continued Cure)**	**No**
151006	73/M	11	No / No TOC urine culture; patient withdrew consent	0.12	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No

TABLE 24
Cipro BID Patients with *Pseudomonas aeruginsa* as a Pathogen in Pre-Therapy Urine Culture

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Valid for Efficacy?	*P. aeruginosa* MIC (μg/mL)	Bacteriological Response to *P. aeruginosa* at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
cUTI Patients							
031024	**81/M**	**14**	**Yes**	**0.12**	**Eradication (Eradication)**	**Cure (Continued Cure)**	**No**
049031	**83/M**	**14**	**Yes**	**0.25**	**Eradication (Recurrence)**	**Cure (Failure)**	**Yes (Macrobid following F/U visit, changed to Cipro)**
064015*	81/M	12	No No TOC urine culture; patient withdrew consent	0.25	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
076002	62/M	11	No Protocol violation; did not have enough clinical symptoms for inclusion	0.25	Eradication (New Infection with *S. aureus*)	Cure (Relapse)	Yes (Cipro following F/U visit)
109002	**52/M**	**12**	**Yes**	**0.12**	**Eradication of *P. aeruginosa*, but New Infection with *E. faecalis* (New Infection)**	**Cure (Not Reported)**	**Yes (ampicillin following F/U visit)**
123003	67/M	15	No Resistant Organism	4	Persistence (Persistence)	Cure (Relapse)	Yes (gentamicin following TOC visit)

* *E. faecalis* also present as pre-therapy pathogen

Reviewer's Comment: The applicant included (b) (4) *and* Pseudomonas aeruginosa *in the "Indications and Usage" section and in the efficacy table in the "Clinical Studies" section of the package insert. At a teleconference on July 10, 2003, the Division asked the applicant to provide information to support the inclusion of these two organisms in the label, since there are less than 10 isolates for each. On July 29, 2003 the applicant submitted the requested information. They indicated that they are withdrawing the proposal to include* (b) (4) *in the "Indications and Usage" and "Clinical Studies" section and will shift the organism to the "second list" in the "Microbiology" section of the package insert.*

Regarding the inclusion of P. aeruginosa *in the XR label, the applicant justified their position with data to support the following: (1)* (b) (4) *ciprofloxacin is indicated for cUTIs, including those caused by susceptible strains of* P. aeruginosa*, (2) an antimicrobial agent selected to treat cUTI should achieve adequate concentrations at the site of infection. Cipro XR 1000 mg tablets have an absolute bioavailability of up to 90% and a relative bioavailability of 98% when compared to the IR formulation. Plasma concentrations are about 40% to 70% greater than the concentrations achieved with 500 mg BID of the immediate-release formulation. In the urine, the XR formulation of ciprofloxacin (1000 mg) achieves significantly higher concentrations of ciprofloxacin than the immediate release formulation (500 mg BID) for up to 12 hours following a dose. Concentrations of both formulations in the urine remain in excess of the MIC values of susceptible pathogens throughout the dosing interval, (3) surveillance data shows that 75% of* P. aeruginosa *isolates from UTIs analyzed between Jan 1st and December 31st 2002, were susceptible to ciprofloxacin, and (4) nine of the 14* P. aeruginosa *isolates identified in the pivotal trial (100275) are susceptible to ciprofloxacin. All nine were clinically cured and bacteriologically eradicated.*

The applicant concludes that a combination of the microbiological data (MICs) for susceptible isolates of P. aeruginosa *along with the achievable concentrations of the drug in plasma and urine, supports Cipro XR ais an appropriate drug to select for the treatment of cUTI caused by susceptible strains of* P. aeruginosa*.*

The applicant also indicated that they would be amenable to conducting a Phase IV study to gather additional isolates of P. aeruginosa*, similar to what the Division requested of them for* Staphylococcus saprophyticus *for the indication of uUTI (Cipro XR 500 mg, NDA 21-473), if the Division would grant them* P. aeruginosa *in the label.*

The reviewer accepts the applicant's rationale for inclusion of P. aeruginosa *in the label, based on the pharmacokinetic and susceptibility data provided. In addition, the applicant will be requested to obtain information on additional isolates of* P. aeruginosa *as a Phase IV commitment.*

4. By Duration of Therapy

Patients were assigned to treatment durations of 7 to 14 days by the individual investigators. Table 25 shows the eradication rates at the TOC visit subgrouped by the actual treatment duration (i.e., some patients took more or less medications than advised). Eradication rates are numerically similar (1) within treatment duration subgroups between study drugs; as well as, (2) within each study drug across different treatment duration subgroups.

Reviewer's Comment: Table 25 was created by the reviewer.

TABLE 25
Eradication (%) at the TOC Visit (+5 to +11 Days)
by Days of Treatment
Patients Valid for Efficacy

	Cipro XR	**Cipro BID**
All Patients	183/206 (88.8%)	195/229 (85.2%)
5 to 7 days	28/31 (90.3%)	24/30 (80.0%)
8 to 10 days	43/48 (89.6%)	43/52 (82.7%)
11 to 15 days	112/127 (88.2%)	128/147 (87.1%)
AUP Patients	35/40 (87.5%)	51/52 (98.1%)
5 to 7 days	3/3 (100%)	4/4 (100%)
> 7 to 10 days	5/7 (71.4%)	7/7 (100%)
10 to 14 days	27/30 (90%)	40/41 (97.6%)
cUTI Patients	148/166 (89.2%)	144/177 (81.4%)
5 to 7 days	25/28 (89.3%)	20/26 (76.9%)
> 7 to 10 days	38/41 (92.7%)	36/45 (80.0%)
10 to 15 days	85/97 (87.6%)	88/106 (83.0%)

Reviewer's Comment: There are two patients in the Cipro BID group that received less than 7 days of treatment (5 days and 6 days, respectively) in the applicant's valid for efficacy population. Both are cUTI patients with persistence of infection at the TOC visit.

5. By Timing of the TOC Visit

The original protocol specified the TOC visit should occur between 5 and 9 days following the last dose of study drug. Amendment number 7 expanded the TOC visit window from 5 to 9 days to 5 to 11 days after the last dose of study drug. An additional 17 patients are included in the valid for efficacy population when the TOC visit window was expanded from 9 days to 11 days after the last dose of study drug. Bacteriologic results for the 17 patients included in the expanded analysis are shown in Table 26. Table 27 presents bacteriologic response rates by timing of the TOC visit (i.e., response for the population with a TOC visit from 5 to 9 days versus 5 to 11 days after the last dose of study drug).

Reviewer's Comment: The applicant's October 29, 2002 submission stated there are an additional 19 patients included in the valid for efficacy population when the TOC visit window was expanded. However, the reviewer only identified 17 patients. In a correspondence dated May 2, 2003 the applicant corrected the number from 19 to 17 and provided a list of patients: 31004, 36003, 42028, 49011, 49057, 53001, 53013, 53018, 53028, 73010, 77018, 91002, 95018, 97001, 105011, 120001, 148019.

Reviewer's Comment: Tables 26 and 27 were created by the reviewer.

TABLE 26
Patients with the TOC visit Occurring between > 9 and 11 Days After the Last Dose of Study Drug

	Cipro XR (N=9)	Cipro BID (N=8)
Patients with bacteriologic eradication cUTI patients eradicated AUP patients eradicated	7 6/8 1/1	7 5/6 2/2
New infection	1 (cUTI)	0
Persistence	1 (cUTI)	1 (cUTI)

TABLE 27
Number of Patients (%) with Eradication by Timing of TOC Visit
Patients Valid for Efficacy

	Cipro XR	**Cipro BID**
All Patients		
+5 to +9 days	176/197 (89.3%)	188/221 (85.1%)
+5 to +11 days	183/206 (88.8%)	195/229 (85.2%)
AUP Patients		
+5 to +9 days	34/39 (87.1%)	49/50 (98.0%)
+5 to +11 days	35/40 (87.5%)	51/52 (98.1%)
cUTI Patients		
+5 to +9 days	142/158 (89.9%)	139/171 (81.3%)
+5 to +11 days	148/166 (89.2%)	144/177 (81.4%)

B. Bacteremias

Of the 435 valid for efficacy patients, 429 (98.6%) had a pre-therapy blood culture obtained. Twelve of the 429 patients had bacteremia caused by *E. coli* (11 patients) and *K. pneumoniae* (1 patient) as shown in Table 28. There are two patients (patient 118021 in the Cipro XR group and patient 82040 in the Cipro BID group) out of the 12 patients with pre-therapy bacteremia in whom blood cultures were not performed at the during therapy visit. The organism isolated in blood was eradicated in 10/10 patients with during therapy blood culture results.

All 12 patients are bacteriologic cures (negative urine culture) and clinical cures at the TOC visit.

Reviewer's Comment: Table 28 was created by the reviewer.

TABLE 28
Patients with Pre-Therapy Bacteremia and Bacteriologic Outcome
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	**Cipro BID**
AUP Patients		
Escherichia coli	4/5*	1/1
Klebsiella pneumoniae	1/1	--
cUTI Patients		
Escherichia coli	1/1	3/4*

*one patient did not have a repeat blood culture during treatment

C. Organisms Causing Super and New Infections

A summary of the organisms causing superinfection or new infection in AUP and cUTI patients valid for efficacy at the TOC visit is presented in Table 29.

TABLE 29
Organisms Causing Superinfection or New Infections in AUP and cUTI Patients Combined at TOC (+5 to +11 Days)
Patients Valid for Efficacy

	Cipro XR	Cipro BID
Superinfection		
Staphylococcus aureus	3	0
Enterococcus faecalis	0	1
Klebsiella pneumoniae	0	1
Pseudomonas aeruginosa	2	1
Alcaligenes faecalis	0	1
New Infection		
Staphylococcus aureus	1	4
Enterococcus species	0	1
Enterococcus faecalis	7	6
Enterococcus faecium	1	0
Escherichia coli	0	1
Proteus mirabilis	0	1
Citrobacter freundii	0	1
Providencia stuartii	1	0
Acinetobacter calcoaceticus	0	1
Comamonas testosteroni	1	0

The applicant indicated that the number of organisms causing superinfections (5 for Cipro XR and 4 for Cipro BID) or new infections (11 for Cipro XR and 15 for Cipro BID) is higher than shown in Table 10 for the corresponding bacteriologic response. This is due to some patients also having persistent organisms. These patients are classified as having a bacteriologic response of persistence and not superinfection or new infection.

There are more superinfections and new infections in the Cipro BID group (N=17 combined) compared to the Cipro XR group (N=10 combined) at the TOC visit for patients with cUTI. A detailed description of these patients can be found in Tables 30 and 31 for Cipro XR and Cipro BID, respectively.

Reviewer's Comment: Tables 30 and 31 were created by the reviewer.

TABLE 30
Cipro XR Patients with cUTI who Experienced
a Superinfection (N=5) or New Infection (N=5) at the TOC Visit
Patients Valid for Efficacy

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (μg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
Superinfection							
31012	77/M	14	*E. faecalis* (pre-therapy)	1	Eradication (Indeterminate)	Failure (Failure)	Yes (gentamicin following TOC)
			P. aerguinosa [a] (TOC)	> 16	Superinfection (Superinfection)		
53027	25/F	15	*K. pneumoniae* (pre-therapy)	0.25	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			P. aerguinosa (during therapy and TOC)	> 16	Superinfection (Superinfection)		
76013	83/F	14	*K. pneumoniae* (pre-therapy)	0.03	Indeterminate (Indeterminate)	Not Reported (Not Reported)	Yes (Macrobid following study drug)
			E. faecium (pre-therapy)	2	Indeterminate (Indeterminate)		
			S. aureus (during therapy)	> 16	Superinfection (Superinfection)		
90121*	96/F	7	*C. freundii* (pre-therapy)	0.12	Eradication (Continued Eradication)	Cure (Relapse)	Yes (Macrodantin at F/U, although F/U urine culture was negative)
			P. mirabilis (pre-therapy)	1	Eradication (Continued Eradication)		
			Comamonas testasteroni (TOC)	16	New infection (New infection)		
			S. aureus (during therapy and TOC)	> 16	Superinfection (Superinfection)		
127001	33/F	15	*E. faecalis* (pre-therapy)	2	Indeterminate (Indeterminate)	Failure (Failure)	Yes (Bactrim DS following study drug)
			K. pneumoniae (pre-therapy)	0.03	Indeterminate (Indeterminate)		
			S. aureus (during therapy)	> 16	Superinfection (Superinfection)		
New Infection							
15018	29/M	8	*P. mirabilis* (pre-therapy)	0.015	Eradication (Indeterminate)	Cure (Relapse)	Yes (Bactrim DS following TOC)
			P. stuartii [c] (TOC)	8	New Infection (New Infection)		
49057	75/F	14	*P. mirabilis* (pre-therapy)	0.06	Eradication (Continued Eradication)	Cure (Relapse)	Yes (Levo at F/U followed by Macrobid)
			E. faecalis (TOC and F/U)	> 16	New Infection (New Infection)		
			E. coli (F/U)	> 16	-- (New Infection)		

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (μg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
73011	41/F	10	*K. pneumoniae* (pre-therapy)	0.03	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			E. faecalis (TOC and F/U)	1	New Infection (New Infection)		
125006	73/F	14	*K. pneumoniae* (pre-therapy)	0.25	Eradication (Indeterminate)	Failure (Failure)	Yes (Bactrim DS following study drug)
			S. aureus (TOC)	8	New Infection (New infection)		
207023	61/F	7	*E. coli* (pre-therapy)	0.015	Eradication (Continued Eradication)	Cure (Relapse)	Yes (Bactrim DS following TOC)
			E. faecalis (TOC and F/U)	> 16	New Infection (New Infection)		

* experienced both a superinfection and a new infection; counted as new infection only by the applicant
[a] pre-therapy urine contained 6,000 CFU/mL of *P. aeruginosa* (regarded as contaminant)

TABLE 31
Cipro BID Patients with cUTI who Experienced
a Superinfection (N=3) or New Infection (N=14) at the TOC Visit
Patients Valid for Efficacy

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (μg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
Superinfection							
35002	46/M	8	*P. mirabilis* [a] (pre-therapy)	0.12	Eradication (Recurrence)	Cure (Continued Cure)	No
			E. faecalis (during therapy)	1	Superinfection (Superinfection)		
			P. mirabilis [b] (F/U)	0.12	--		
90077	91/M	8	*P. mirabilis* (pre-therapy)	0.5	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
			P. aeruginosa [c] (during therapy)	> 16	Superinfection (Superinfection)		
			K. pneumoniae (during therapy)	> 16	Superinfection (Superinfection)		
127007	32/M	14	*Providencia rettgeri* (pre-therapy)	0.03	Indeterminate (Continued Eradication)	Cure (Continued Cure)	No
			Alcaligenes faecalis (during therapy)	> 16	Superinfection (Superinfection)		
			P. aerguinosa (F/U)	2	Superinfection (New Infection)		
New Infection							
15003	47/M	7	*E. coli* (pre-therapy)	0.12	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Bactrim DS following

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (μg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
			S. aureus (TOC)	> 16	New Infection (New Infection)		TOC)
15016	32/M	7	*P. mirabilis (pre-therapy)*	0.03	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Bactrim DS following TOC)
			S. aureus (TOC)	16	New Infection (New Infection)		
29042	37/F	14	*S. aureus* (pre-therapy)	0.5	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			E. faecalis (TOC and F/U)	1	New Infection (New Infection)		
39005	75/M	7	*E. faecalis* (pre-therapy)	1	Eradication (Indeterminate)	Cure (Not Reported)	No
			S. aureus (TOC)	> 16	New Infection (New Infection)		
42022	81/M	14	*E. coli* (pre-therapy)	1	Eradication (Indeterminate)	Cure (Not Reported)	No
			E. faecalis [d] (TOC)	0.5	New Infection (New Infection)		
48013	72/F	15	*E. coli* (pre-therapy)	0.03	Eradication (Indeterminate)	Failure (Failure)	No
			E. faecalis (TOC)	> 16	New Infection (New Infection)		
59033	63/F	7	*K. pneumoniae* [e] (pre-therapy)	0.5	Eradication (Indeterminate)	Failure (Failure)	Yes (Bactrim DS at TOC)
			E. coli (TOC)	> 16	New Infection (New Infection)		
74002	87/F	14	*P. mirabilis* (pre-therapy)	2	Eradication (Recurrence)	Cure (Continued Cure)	No
			E. faecalis (TOC)	> 16	New Infection (New Infection)		
			P. mirabilis (F/U)	2	--		
76008	90/M	10	*Citrobacter koseri* (pre-therapy)	0.015	Eradication (Indeterminate)	Cure (Relapse)	Yes (Macrobid following TOC)
			E. faecalis (TOC)	> 16	New Infection (New Infection)		
92011	82/F	14	*S. marcescens* (pre-therapy)	1	Eradication (Indeterminate)	Failure (Failure)	No
			E. faecalis (pre-therapy)	1	Eradication (Indeterminate)		
			P. mirabilis (TOC)	2	New Infection (New Infection)		
95009	57/F	14	*K. pneumoniae*	0.06	Eradication (Continued Eradication)	Cure (Failure)	Yes (Macrobid at F/U)
			Acinetobacter calcoaceticus (TOC)	Not reported	New Infection (New Infection)		

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (μg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
			Enterococcus sp. (TOC)	Not reported	New Infection (New Infection)		
			E. faecalis (F/U)	0.5	--		
			E. coli (F/U)	0.12	--		
109002	52/M	12	*P. aeruginosa* (pre-therapy)	0.12	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Ampicillin at following TOC)
			E. faecalis (TOC)	> 16	New Infection (New Infection)		
115001	30/M	14	*K. pneumoniae* [f] (pre-therapy)	0.06	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Doxycycline following TOC)
			C. freundii [g] *(TOC)*	4	New Infection (New Infection)		
137002	50/F	14	*E. coli* (pre-therapy)	0.015	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			S. aureus (TOC)	> 16	New Infection (New Infection)		

[a] Pre-therapy urine culture also contained 60,000 CFU/mL of *E. cloacae* (MIC 0.015 μg/mL)
[b] F/U urine culture also contained 20,000 *E. faecalis* (MIC 0.5 μg/mL)
[c] During therapy urine culture also contained 20,000 *E. faecalis* (MIC > 16 μg/mL)
[d] TOC urine culture also contained 35,000 CFU/mL of *P. mirabilis* (MIC 0.03 μg/mL)
[e] Pre-therapy urine culture also contained 50,000 CFU/mL of *S. marcescens* (0.12 μg/mL)
[f] Pre-therapy urine culture also contained 20,000 CFU/mL of *E. faecalis* (MIC 1 μg/mL)
[g] TOC urine culture also contained 15, 000 CFU/mL of *Acinetobacter* sp. (MIC 4 μg/mL)

D. Eradication at the Late Follow-up Visit

Bacteriological response at the late follow-up visit (+28 to +42 days) is a secondary efficacy variable and the results are shown in Table 32. Eradication is 69.3% in the Cipro XR group and 61.2% in the ciprofloxacin BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (–0.8%, 18.6%) is above -10%. The 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-2.2%, 18.4%).

Reviewer's Comment: Patients with indeterminate responses are specified in the protocol as excluded from valid for efficacy analysis. Therefore, the eradication rates at follow-up in this analysis population do not include the 68 indeterminate responses (27/206 [13.1%] in the Cipro XR group and 41/229 [17.9%] in the Cipro BID group).

TABLE 32
Number of Patients (%) with Bacteriological Response at the Follow-up Visit (+28 to +42 Days)
Patients Valid for Efficacy

	Cipro XR	**Cipro BID**
All Patients	(N=206)	(N=229)
Continued eradication	124 (60.2%)	115 (50.2%)
Eradication w/recurrence	19 (9.2%)	18 (7.9%)
Persistence	10 (4.9%)	17 (7.4%)
Superinfection	5 (2.4%)	2 (0.9%)
New infection	21 (10.2%)	36 (15.7%)
Indeterminate	27 (13.1%)	41 (17.9%)
Eradication Rate[a]	**124/179 (69.3%)**	**115/188 (61.2%)**
AUP Patients	(n=40)	(n=52)
Continued eradication	25 (62.5%)	35 (67.3%)
Eradication w/recurrence	1 (2.5%)	3 (5.8%)
Persistence	2 (5.0%)	1 (1.9%)
New infection	5 (12.5%)	4 (7.7%)
Indeterminate	7 (17.5%)	9 (17.3%)
Continued Eradication Rate[b]	**25/33 (75.8%)**	**35/43 (81.4%)**
cUTI Patients	(n=166)	(n=177)
Continued eradication	99 (59.6%)	80 (45.2%)
Eradication w/recurrence	18 (10.8%)	15 (8.5%)
Persistence	8 (4.8%)	16 (9.0%)
Superinfection	5 (3.0%)	2 (1.1%)
New infection	16 (9.6%)	32 (18.1%)
Indeterminate	20 (12.0%)	32 (18.1%)
Continued Eradication Rate[c]	**99/146 (67.8%)**	**80/145 (55.2%)**

[a] Eradication rate for all patients (cUTI plus AUP); the follow-up rates in this population do not include the indeterminate responses. 95% Confidence Interval: (-0.8%, 18.6%)
[b] Continued eradication rate for AUP patients, not including indeterminate responses.
[c] Continued eradication rate for cUTI patients, not including indeterminate responses.

The bacteriologic eradication rates at the late follow-up visit in AUP patients are lower in the Cipro XR group (62.5%, 25/40) compared to the Cipro BID group (67.3%, 35/52). In cUTI patients, the rates are higher in the Cipro XR group (59.6%, 99/166) compared to the Cipro BID group (45.2%, 80/177). The differences between the two patient groups follows a similar trend to the results at the TOC visit.

Reviewer's Comment: For the analysis of bacteriologic eradication at the late follow-up visit performed on the MITT population (all patients with a pathogen identified at baseline), see statistical review (Ruthana Davi, M.S., statistical reviewer).

Reviewer's Comment: One patient in the Cipro BID group (35002) who was counted in the superinfection category at the TOC visit (see Table 10) was

subsequently counted in the category eradication with recurrence (not superinfection) at the follow-up visit (see Table 26). The baseline pathogen for this patient was P. mirabilis, and E. faecalis was isolated during therapy (superinfection). At the TOC visit, P. mirabilis was eradicated and E. faecalis was absent. At the follow-up visit, P. mirabilis again was isolated from urine, and the patient was included in the response category eradication with recurrence by the applicant rather than being carried forward as superinfection. The reviewer agrees with this assessment.

Reviewer's Comment: For the analysis of bacteriologic eradication at the late follow-up visit performed on the MITT population (all patients with a pathogen identified at baseline), see statistical review (Ruthana Davi, M.S., statistical reviewer).

E. By Organism

The bacteriologic response rates by organism at the follow-up visit in patients valid for efficacy are shown in Table 33.

TABLE 33
Bacteriological Response at Follow-up (+28 to +42 Days) by Organism
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	**Cipro BID**
AUP Patients		
Escherichia coli	27/28 (96%)	33/34 (97%)
cUTI Patients		
Escherichia coli	74/87 (85%)	60/72 (83%)
Klebsiella pneumoniae	13/16 (81%)	12/16 (75%)
Enterococcus faecalis	10/12 (83%)	7/16 (44%)
Proteus mirabilis	9/11 (82%)	6/8 (75%)

Except for *E. coli*, eradication rates for patients with cUTI are slightly higher in the Cipro XR group than in the Cipro BID group. In both treatment arms, eradication rates decreased from the TOC time point to the follow-up time point.

F. Organisms Causing Super and New Infections

A summary of the organisms causing superinfection or new infection in patients valid for efficacy at follow-up is presented in Table 34. The results include the numbers of superinfections and new infections at the TOC carried forward as well as superinfections and new infections at follow-up.

Reviewer's Comment: Table 34 is modified from the applicant's submission by the reviewer for clarity.

TABLE 34
Organisms Causing Superinfection or New Infections at Follow-up (+28 to +42 Days) Patients Valid for Efficacy

	Cipro XR	Cipro BID
Superinfection		
S. aureus	3	0
E. faecalis	0	1
K. pneumoniae	0	1
P. aeruginosa	2	1
A. faecalis	0	1
New Infection		
S. aureus	4	4
S. saprophyticus	1	0
Enterococcus sp.	0	2
E. faecalis	14	17
E. faecium	1	0
E. coli	4	4
K. pneumoniae	0	7
K. oxytoca	1	0
P. mirabilis	0	1
C. freundii	1	2
C. amalonaticus	0	1
P. stuartii	1	0
P.aeruginosa	1	2
A. calcoaceticus	0	1
C. testosteroni	1	0

The number of organisms causing superinfections (5 for Cipro XR and 4 for Cipro BID) or new infections (29 for Cipro XR and 41 for Cipro BID) is higher than shown in Table 32 for the corresponding bacteriologic response. This is due to some patients also having persistent organisms. These patients are classified as having a bacteriologic response of persistence and not superinfection or new infection.

Of the 39 new infecting organisms recovered after the TOC time point, 18 are identified as *E. faecalis* (7 from patients in the Cipro XR group and 11 from patients in the Cipro BID group), 7 are identified as *E. coli* (4 and 3, respectively) and 7 are identified as *K. pneumoniae* (0 and 7, respectively). There are more patients in the Cipro BID group than in the Cipro XR group who had new infecting organisms isolated between the TOC and follow-up visits (17 in the Cipro XR group versus 26 in the Cipro BID group).

VI. Efficacy Results for the Valid for Efficacy Population – Clinical Response

A. Clinical Response at the TOC Visit

The clinical response rate at the TOC visit is a secondary efficacy parameter and the results in patients valid for efficacy are shown in Table 35. Eradication is 96.6% in the Cipro XR group and 93.8% in the ciprofloxacin BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (–1.2%, 6.9%) is above -10%. The 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-1.7%, 7.3%).

TABLE 35
Number of Patients (%) with Clinical Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Efficacy

	Cipro XR	**Cipro BID**
All Patients	(N=206)	(N=229)
Cure	198 (96.1%)	211 (92.1%)
Failure	7 (3.4%)	14 (6.1%)
Indeterminate	0 (0.0%)	1 (0.4%)
Missing	1 (0.5%)	3 (1.3%)
Success Rate[a]	**198/205 (96.6%)**	**211/225 (93.8%)**
AUP Patients	(n=40)	(n=52)
Cure	39 (97.5%)	50 (96.2%)
Failure	1 (2.5%)	2 (3.8%)
cUTI Patients	(n=166)	(n=177)
Cure	159 (95.8%)	161 (91.0%)
Failure	6 (3.6%)	12 (6.8%)
Indeterminate	0 (0.0%)	1 (0.6%)
Missing	1 (0.6%)	3 (1.7%)
Success Rate[b]	**159/165 (96.4%)**	**161/173 (93.1%)**

[a] Success rate for all patients (cUTI plus AUP), not including indeterminate or missing responses; 95% Confidence Interval: (-1.2%, 6.9%)
[b] Success rate for patients with cUTI, not including indeterminate or missing responses

Reviewer's Comment: The clinical cure rates for AUP and cUTI patients separately were calculated by the statistical reviewer.

The clinical cure rates for the AUP patients are similar in the Cipro XR group (97.5%) to the Cipro BID group (96.2%) [corresponding 97.5% confidence interval of the difference (-15.3%, 21.1%)]. In the cUTI group clinical cure rates are also similar between the Cipro XR group (95.8%) and the Cipro BID group (91.0%) [corresponding 97.5% confidence interval of the difference* (-1.1, 10.8%)]. *When calculating the results of each stratum alone an adjustment must be made for multiple comparisons (i.e., use of 97.5% confidence intervals for the differences between Cipro XR and Cipro BID within the AUP and cUTI subgroups).*

Reviewer's Comments: Patients with indeterminate responses are specified in the protocol as excluded from valid for efficacy analysis. Only one cUTI patient in the Cipro BID group had an indeterminate clinical response at the TOC visit.

Each of the clinical signs and symptoms present initially must be rated as 0 (none present) in order to be considered a clinical cure. In a few of the 10% random sample, the patients considered to be clinical cures by the Investigator still had signs and or symptoms present at the TOC visit that were present at baseline, but these may have been due to the patient's underlying condition(s) and not infection.

The results for clinical response are consistent with the results for bacteriological response within treatment groups for the category "All Patients" in the valid for efficacy population at the TOC visit as seen in Table 36. However, for patients with AUP who were treated with Cipro XR, there is a 10% difference between the eradication rate (87.5%) and the clinical cure rate (97.5%) at the TOC visit.

Reviewer's Comment: Table 36 was created by the reviewer.

TABLE 36
Comparison of Bacteriologic and Clinical Success Rates
at the TOC Visit (+5 to +11 Days)
Patients Valid of Efficacy

	n/N (%)			
	Cipro XR		**Cipro BID**	
	Bacteriologic	Clinical	Bacteriologic	Clinical
All Patients	183/260 (88.8)	198/205 (96.6)	195/229 (85.2)	211/225 (93.8)
AUP Patients	35/40 (87.5)	39/40 (97.5)	51/51 (98.1)	50/52 (96.2)
cUTI Patients	148/166 (89.2)	159/165 (96.4)	144/177 (81.4)	161/173 (93.1)

A summary of clinical response by bacteriological response at the TOC visit for patients valid for efficacy is shown in Table 37. There are somewhat fewer discordant observations in the Cipro XR group than in the Cipro BID group. For 91% of patients in the Cipro XR group and 88% of patients in the Cipro BID group, the clinical and bacteriological response assessments are both either successful outcomes or unsuccessful outcomes.

TABLE 37
Clinical Response by Bacteriological Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Efficacy

Bacteriological Response	Clinical Response	Cipro® XR	Cipro®BID
Eradication	Cure	182 (99.5%)	191 (97.9%)
	Failure	1 (0.5%)	3 (1.5%)
	Indeterminate	0 (0.0%)	1 (0.5%)
Persistence	Cure	7 (70.0%)	7 (41.2%)
	Failure	3 (30.0%)	8 (47.1%)
	Missing	0 (0.0%)	2 (11.8%)
Superinfection	Cure	2 (40.0%)	2 (66.7%)
	Failure	2 (40.0%)	0 (0.0%)
	Missing	1 (20.0%)	1 (33.3%)
New infection	Cure	7 (87.5%)	11 (78.6%)
	Failure	1 (12.5%)	3 (21.4%)

B. Clinical Response at the Follow-up Visit

The clinical response rate at the follow-up visit is a secondary efficacy parameter and the results in patients valid for efficacy is shown in Table 38. Eradication is 82.9% in the Cipro XR group and 80.8% in the ciprofloxacin BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (–5.4%, 10.4%) is above –10%. The 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-6.3%, 10.6%).

Reviewer's Comment: Patients with indeterminate responses are specified in the protocol as excluded from valid for efficacy analysis. Therefore, the eradication rates at follow-up in this analysis population do not include the 68 indeterminate responses (27/206 [13.1%] in the Cipro XR group and 41/229 [17.9%] in the Cipro BID group).

TABLE 38
Number of Patients (%) with Clinical Response at the Follow-up Visit (+28 to +42 Days)
Patients Valid for Efficacy

	Cipro XR	**Cipro BID**
All Patients	(N=206)	(N=229)
Continued cure	150 (72.8%)	151 (65.9%)
Failure	8 (3.9%)	16 (7.0%)
Relapse	23 (11.2%)	20 (8.7%)
Indeterminate	2 (1.0%)	3 (1.3%)
Missing	23 (11.2%)	39 (17.0%)
Success Rate[a]	**150/181 (82.9%)**	**151/187 (80.8%)**
AUP Patients	(n=40)	(n=52)
Continued cure	30 (75.0%)	42 (80.8%)
Failure	1 (2.5%)	2 (3.8%)
Relapse	5 (12.5%)	0 (0.0%)
Missing	4 (10.0%)	8 (15.4%)
Success Rate[b]	**30/36 (83.3%)**	**42/44 (95.5%)**
cUTI Patients	(n=166)	(n=177)
Continued cure	120 (72.3%)	109 (61.6%)
Failure	7 (4.2%)	14 (7.9%)
Relapse	18 (10.8%)	20 (11.3%)
Indeterminate	2 (1.2%)	3 (1.7%)
Missing	19 (11.4%)	31 (17.5%)
Success Rate[c]	**120/145 (82.8%)**	**109/143 (76.2%)**

[a] Success rate for all patients (cUTI plus AUP), not including missing or indeterminate responses; 95% Confidence Interval: (-5.4%, 10.4%)
[b] Success rate for pyelonephritis patients, not including missing responses.
[c] Success rate for complicated UTI patients, not including missing or indeterminate responses.

The clinical response at the late follow-up visit in AUP patients is slightly lower for the Cipro XR group (75%, 30/40) compared to Cipro BID group (80.8%, 42/52). In cUTI patients, the response rates are slightly higher in the Cipro XR group (72.3%, 120/166) compared to the Cipro BID group (61.6%, 109/177).

The results for clinical response are lower than the results for bacteriological response in the valid for efficacy population at the follow-up visit as seen in Table 39.

Reviewer's Comment: Table 39 was created by the reviewer.

TABLE 39
Comparison of Bacteriologic and Clinical Success Rates
at the Follow-Up Visit (+28 to +42 Days)
Patients Valid of Efficacy

	n/N (%)			
	Cipro XR		Cipro BID	
	Bacteriologic	Clinical	Bacteriologic	Clinical
All Patients	124/179 (69.3)	150/181 (82.9)	115/188 (61.2)	151/187 (80.8)
AUP Patients	25/33 (75.8)	30/36 (83.3)	35/43 (81.4)	42/44 (95.5)
cUTI Patients	99/146 (67.8)	120/145 (82.8)	80/145 (55.5)	109/143 (76.2)

VII. Post-Treatment Antimicrobial Use

Twenty-three (23) percent of patients valid for efficacy in both treatment groups used at least one post-treatment antimicrobial agent at some point from one day after the end of therapy through the end of the long-term follow-up period. Antimicrobials were used for urinary tract infections as well as other types of infections. The most common post-therapy antimicrobial drugs used were ciprofloxacin (7% in Cipro XR group and 8% in Cipro BID group), nitrofurantoin (6% in the Cipro XR group and 4% in the Cipro BID group), and levofloxacin (5% in the Cipro XR group and 3% in the Cipro BID group).

VIII. Efficacy Results for the Applicant's Valid for Safety (Intent to Treat) Population – Bacteriologic and Clinical Response

Efficacy variables for patients valid for safety are presented in Tables 40-43 in Appendix 2. The main differences between the valid for safety population and the valid for efficacy population occurred in the bacteriological responses and clinical responses at the TOC visit. In the valid for safety analysis population, eradication rates at the TOC visit are 63.3% and 67.9% in the Cipro XR and Cipro BID group, respectively, as shown in Table 40. The 95% confidence interval for the difference in response between the two treatments at this time point is (-11.8%, 2.9%). The clinical cure rates at the TOC visit are 66.3% and 70.9% for the respective treatment groups as shown in Table 42 and the 95% confidence interval is (-10.1%, 1.2%).

These differences are caused mainly by inclusion of indeterminate bacteriological responses and indeterminate or missing clinical responses that are excluded from the analyses of the valid for efficacy population. The Cipro XR group has more patients with an indeterminate bacteriological response at TOC as compared to the Cipro BID group (82 [25.1%] versus 49 [15.6%] patients; Table 40). Approximately 50% of the patients have data outside the window for the TOC visit or have no data at the TOC visit. Although the Cipro BID group has a higher percentage of patients with an outcome of persistence, superinfection, or new infection (38 [11.6%] in the Cipro XR group versus 52 [16.5%] in the Cipro BID group), the inclusion of indeterminate responses as nonsuccesses lowered the eradication rate disproportionately in the Cipro XR group.

The clinical cure rate at TOC is affected in a similar manner by inclusion of missing clinical responses as nonsuccesses. More patients in the Cipro XR group (138 [26.7%]) than in the Cipro BID group (111 [21.4%]; Table 36) have a missing or indeterminate clinical response. Therefore, the clinical cure rate appeared to be lower in the Cipro XR treatment group.

The discrepancy between the two treatment groups in terms of the distribution of patients with missing or indeterminate responses is still present, but to a lesser extent, at follow-up for the valid for safety population.

IX. Efficacy Results for Special Populations – Bacteriologic Response

Subgroup analyses were performed on data for the valid for efficacy population to explore potential drug-demographic interactions based on age, sex, and race.

A. Age

Bacteriological response by age at the TOC visit is summarized in Table 44. For patients treated with Cipro XR, the bacteriologic eradication rates are lower in patients less than 65 years of age [85.0% (85/100)] compared to those 65 years of age and older [92.4% (98/106)] at the TOC visit. Less efficacy in the younger patients may be a result of the lower bacteriological response in AUP patients [87.5% 935/40] compared to cUTI patients [89.2% (148/166)]. Patients treated with Cipro XR in the AUP sub-group are younger (mean age 41 years) compared with cUTI (mean age 64 years).

Although younger patients treated with Cipro XR have lower eradication rates [85.0% (85/100)] than older patients treated with Cipro XR, the efficacy in this age group is similar to patients treated with Cipro BID [84.1% (90/107)]. Patients receiving Cipro BID responded similarly, regardless of age [84.1% (90/107) eradication for those < 65 years and 86.1% (105/122) for those ≥ 65 years].

Reviewer's Comment: The differences seen in bacteriologic eradication between younger and older patients is not considered clinically relevant and no adjustments to the dosing of Cipro XR are warranted based on age.

TABLE 44
Number of Patients (%) with Bacteriological Response by Age (in years) at the TOC Visit (+5 to +11 Day)
Patients Valid for Efficacy

	Cipro XR				Cipro BID			
	< 65 N=100	≥ 65 N=106	65-74 N=44	≥ 75 N=62	<65 N=107	≥ 65 N=122	65-74 N=49	≥ 75 N=73
Eradication	85 (85.0)	98 (92.4)	42 (95.5)	56 (90.3)	90 (84.1)	105 (86.1)	40 (81.6)	65 (89.0)
Persistence	7 (7.0)	3 (2.8)	1 (2.3)	2 (3.2)	7 (6.5)	10 (8.2)	8 (16.3)	2 (2.7)
Superinfection	2 (2.0)	3 (2.8)	0 (0.0)	3 (4.8)	2 (1.9)	1 (0.8)	0 (0.0)	1 (1.4)
New Infection	6 (6.0)	2 (1.9)	1 (2.3)	1 (1.6)	8 (7.5)	6 (4.9)	1 (2.0)	5 (6.8)

B. Sex

Bacteriological response by sex at the TOC visit is summarized in Table 45. Male patients [92.0% (81/88)] have a higher bacterial eradication rate than female patients [86.4% 102/118)] treated with Cipro XR at the TOC visit. The reverse situation is true for Cipro BID where female patients [89.8% (114/127)] have a higher eradication rate than male patients [79.4% (81/102)]. The difference in the Cipro XR group appears to be due to a higher number of female patients with superinfections and new infections.

Although the female patients treated with Cipro XR have lower eradication rates [86.4% (102/118)] than male patients treated with Cipro XR, the efficacy in this group is similar to female patients treated with Cipro BID [89.8% (114/127)] and higher than male patients treated with Cipro BID [79.4% (81/102)].

Reviewer's Comment: The differences seen in bacteriologic eradication between males and females patients is not considered clinically relevant and no adjustments to the dosing of Cipro XR are warranted based on sex.

TABLE 45
Number of Patients (%) with Bacteriological Response by Sex at the TOC Visit (+5 to +11 Day)
Patients Valid for Efficacy

	Cipro XR		Cipro BID	
	Male N=88	Female N=118	Male N=102	Female N=127
Eradication	81 (92.0%)	102 (86.4%)	81 (79.4%)	114 (89.8%)
Persistence	5 (5.7%)	5 (4.2%)	11 (10.8%)	6 (4.7%)
Superinfection	1 (1.1%)	4 (3.4%)	3 (2.9%)	0 (0.0%)
New Infection	1 (1.1%)	7 (5.9%)	7 (6.9%)	7 (5.5%)

C. Race

Bacteriological response by race at the TOC visit is summarized in Table 46. Most of the valid for efficacy patients are Caucasian [79% (345/435)]. Among patients who are not Caucasian, most are categorized as Black or Hispanic [20% (88/435)]. Less than 1% of patients in each treatment group are Asian. Eradication rates for both Cipro XR and Cipro BID appear similar for Caucasian and Black patients. Hispanic patients appear to have higher eradication rates. There are too few Asian patients in the study to make an assessment on eradication.

Reviewer's Comment: The differences seen in bacteriologic eradication between patients of different ethnic backgrounds are not considered clinically relevant and no adjustments to the dosing of Cipro XR are warranted based on race.

TABLE 46
Number of Patients (%) with Bacteriological Response by Race at the TOC Visit (+5 to +11 Day)
Patients Valid for Efficacy

	Cipro XR			
	Caucasian N=168	Asian N=1	Hispanic N=18	Black N=19
Eradication	148 (88.1%)	1 (100.0%)	17 (94.4%)	17 (89.5%)
Persistence	10 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Superinfection	4 (2.4%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
New infection	6 (3.6%)	0 (0.0%)	1 (5.6%)	1 (5.3%)
	Cipro BID			
	Caucasian N=177	Asian N=1	Hispanic N=24	Black N=27
Eradication	149 (84.2%)	1 (100.0%)	23 (95.8%)	22 (81.5%)
Persistence	16 (9%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
Superinfection	3 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
New infection	9 (5.1%)	0 (0.0%)	1 (4.2%)	4 (14.8%)

X. Safety Analyses

Of the 1042 patients enrolled into the study, 1035 received at least one dose of study drug (517 in the Cipro XR group and 518 in the Cipro BID group). Seven patients (4 in the Cipro XR group and 3 in the Cipro BID group) are not included in the valid for safety population because study drug administration in these patients could not be documented.

A. Overview

An overview of patients who experienced various safety events is summarized in Table 47. The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups. In addition, rates of drug-related events, serious events, and premature discontinuation due to adverse events are nearly the same in both treatment groups. More patients in the Cipro XR group

(28 patients) than in the Cipro BID group (19 patients) discontinued study drug due to an adverse event.

TABLE 47
Summary of Adverse Events
Patients Valid for Safety

	Cipro XR (N=517)	Ciprofloxacin BID (N=518)
Survived	514 (99.4%)	517 (99.8%)
Any adverse event	165 (31.9%)	165 (31.9%)
Any drug-related adverse event	68 (13.2%)	70 (13.5%)
Any serious adverse event	28 (5.4%)	25 (4.8%)
Discontinuation due to adverse event	28 (5.4%)	19 (3.7%)

Reviewer's Comment: The applicant has proposed to reduce the dosage of Cipro XR 1000 mg in patients with severe renal impairment to Cipro XR 500 mg. This is acceptable to the FDA Clinical Pharmacology and Biopharmaceutics reviewer. However, the issue of dosage adjustment of Cipro XR 1000 mg in cUTI and AUP patients with mild to moderate renal impairment has not been addressed by the applicant in this NDA. Since there is no pharmacokinetic data in patients with mild to moderate renal impairment, it is unknown if the C_{max} and AUC following administration of Cipro XR 1000 mg to would result in excessive drug exposure and a higher incidence of adverse events.

To address this question, the reviewer compared the adverse events reported for patients in the valid for safety population with normal renal function [i.e., a creatinine clearance (CLcr) above 80 mL/min] to the adverse events reported for those with mild to moderate renal impairment [CLcr from 50 to 50 mL/min] in both treatment arms of the study. In Appendix 2, Tables 47A and 47B provide an overview of adverse events in these two subgroups and Tables 48A and 48B detail specific events occurring in at least two patients per treatment arm within the subgroups.

Upon review of these data, the reviewer does not feel that the overall incidence of adverse events or incidence of specific adverse events is different between the two subgroups. In conjunction with the Clinical Pharmacology and Biopharmaceutics reviewer (Dakshina Chilukuri, Ph.D.), the reviewer felt that for AUP and cUTI patients with mild to moderate renal impairment, no dosage adjustment if Cipro XR 1000 mg is recommended, at this time. The applicant will be asked to perform Monte-Carlo simulations to simulate exposure of Cipro XR 1000 mg (administered once daily for 14 days) to patients with mild and moderate renal impairment as a Phase IV commitment. Based on these results, changes in labeling may be recommended at a later time.

B. Adverse Events

A summary of adverse events by body system for each treatment group is presented in Table 49. The most common adverse events in both treatment groups occur in the digestive body system. The incidence of adverse events for

each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30 patients) experienced at least one adverse event involving the nervous system compared with 4% (20 patients) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [<1%] versus 0 patients [0%], respectively).

TABLE 49
Incidence Rates of Adverse Events by Body System
Patients Valid for Safety

Body System	Cipro XR (N=517)		Cipro BID (N=518)	
Any body system	165	(32%)	165	(32%)
Body as a whole	54	(10%)	58	(11%)
Cardiovascular	20	(4%)	16	(3%)
Digestive	71	(14%)	67	(13%)
Hemic and lymphatic	5	(<1%)	4	(<1%)
Metabolic & nutritional	8	(2%)	3	(<1%)
Musculoskeletal	6	(1%)	12	(2%)
Nervous	30	(6%)	20	(4%)
Respiratory	19	(4%)	21	(4%)
Skin and appendages	10	(2%)	10	(2%)
Special senses	7	(1%)	5	(<1%)
Urogenital	39	(8%)	34	(7%)

A summary of adverse events experienced by at least 2% of patients in at least one treatment group is presented in Table 50. The incidence of patients with adverse events generally is similar between treatment groups, with no event having more than a 1% difference between groups, except for headache (3% in the Cipro XR group versus 5% in the Cipro BID group).

TABLE 50
Incidence Rates of Adverse Events Occurring in at Least 2% of Patients in Either Treatment Group
Patients Valid for Safety

Adverse Event	Cipro XR (N=517)		Cipro BID (N=518)	
Any Body System				
Any event	165	(32%)	165	(32%)
Body as a Whole				
Headache	17	(3%)	25	(5%)
Digestive				
Nausea	24	(5%)	23	(4%)
Diarrhea	15	(3%)	11	(2%)
Vomiting	14	(3%)	8	(2%)
Dyspepsia	9	(2%)	6	(1%)
Constipation	5	(<1%)	9	(2%)
Nervous				
Dizziness	16	(3%)	10	(2%)
Urogenital				
Vaginal moniliasis	10	(2%)	8	(2%)

C. Drug-Related Adverse Events

Drug-related adverse events are defined as events considered by the investigator to be possibly or probably related to study drug. Sixty-eight (68) of the 165 patients in the Cipro XR group and 70 of the 165 patients in the Cipro BID group who experienced treatment-emergent adverse events had at least one event that was assessed by the investigator as possibly or probably related to study drug. A summary of drug-related adverse events experienced by at least 1% of patients in either treatment group is presented in Table 51. The incidence rates of drug-related adverse events are similar between the two treatment groups. Nausea and diarrhea are the most common drug-related adverse events.

TABLE 51
Incidence Rates of Drug-Related Adverse Events Occurring in at Least 1% of Patients in Either Treatment Group
Patients Valid for Safety

Adverse Event	Cipro XR (N=517)	Cipro BID (N=518)
Any Body System		
Any event	68 (13%)	70 (14%)
Body as a Whole		
Headache	7 (1%)	8 (2%)
Digestive		
Nausea	15 (3%)	15 (3%)
Diarrhea	12 (2%)	7 (1%)
Dyspepsia	7 (1%)	5 (<1%)
Vomiting	7 (1%)	4 (<1%)
Liver function tests abnormal	1 (<1%)	7 (1%)
Nervous		
Dizziness	9 (2%)	3 (<1%)
Urogenital		
Vaginal moniliasis	9 (2%)	7 (1%)

D. Adverse Events by Intensity

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event that was assessed by the investigator as severe in intensity. The type of severe adverse events by treatment group is shown in Table 52. The number of severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Reviewer's Comment: Table 52 was created by the reviewer.

TABLE 52
Number of Severe Adverse Events by Treatment Group in the Valid for Safety Population

	CIPRO XR	**CIPRO 500 BID**
ABDOMINAL PAIN	1	0
ABORTION	0	1
ACCIDENTAL INJURY	0	1
ACUTE KIDNEY FAILURE	1	1
ACUTE LEUKEMIA	0	1
ANEMIA	2	0
APNEA	1	0
ARTHRITIS	0	1
ASTHMA	1	1
BACK PAIN	1	1

	CIPRO XR	CIPRO 500 BID
BLADDER CARCINOMA	1	0
BODY AS A WHOLE SURGERY	1	0
CARCINOMA	1	2
CHEST PAIN	0	1
COLITIS	2	0
CONGESTIVE HEART FAILURE	2	0
CONSTIPATION	1	0
CORONARY ARTERY DISORDER	0	1
CYST (Baker's cyst, left knee)	1	0
DEEP THROMBOPHLEBITIS	0	1
DEHYDRATION	1	0
DIARRHEA	2	3
DIGESTIVE SURGERY	1	0
DIZZINESS	0	1
DYSPEPSIA	0	3
DYSPNEA	1	0
FEVER	0	1
FLANK PAIN	1	0
GASTROINTESTINAL DISORDER	1	0
GGTP INCREASED	0	1
GRANULOMA	1	0
HEADACHE	1	1
HEMATURIA	4	1
HEMORRHAGE	0	1
HYDRONEPHROSIS	1	0
HYPERTENSION	1	0
HYPERTONIA	0	1
HYPOVENTILATION	1	0
KIDNEY CALCULUS	3	0
KIDNEY FUNCTION ABNORMAL	0	1
KIDNEY PAIN	1	1
LARYNGEAL NEOPLASIA	1	0
LE SYNDROME (Systemic Lupus Erythematosus)	1	0
LEG PAIN	0	1
LIVER FUNCTION TESTS ABNORMAL	0	3
MYOCARDIAL INFARCT	0	1
NAUSEA	2	1
RECTAL HEMORRHAGE	0	1
SEPSIS	0	1
SMALL INTESTINE PERFORATION	0	1
STUPOR	1	0
URINARY RETENTION	4	0
URINARY TRACT INFECTION	1	1
UROGENITAL SURGERY	1	1
VOMITING	3	1
Total	**50**	**39**

E. Discontinuations

No action was taken as a result of more than 40% of all adverse events. A summary of the actions that were taken in response to adverse events is shown in Table 53. Except for a higher rate of study drug discontinuation in the Cipro XR group (i.e., 13.7% compared to 8.9% in the Cipro BID group), the distribution of actions taken for adverse events is similar overall between the two groups.

TABLE 53
Summary of Actions Taken for Adverse Events
Patients Valid for Safety

	Cipro XR 342 Adverse Events	Cipro BID 304 Adverse Events
None	140 (40.9%)	141 (46.4%)
Remedial drug therapy*	116 (33.9%)	97 (31.9%)
Discontinuation of study drug	47 (13.7%)	27 (8.9%)
Hospitalization	35 (10.2%)	30 (9.9%)
Other	47 (13.7%)	36 (11.8%)

Note: Number of actions taken for adverse events is greater than the number of adverse events because some events required more than one action.
*Remedial drug therapy = patient's treated with alternative antimicrobial(s)

A summary of the adverse events causing discontinuation of study drug are shown in Tables 54A and 54B.

Reviewer's Comment: Tables 54A and 54B were created by the reviewer.

Reviewer's Comment: The number of patient discontinuations due to an adverse event is higher in the Cipro XR group (5.4%; 28/517) compared to the Cipro BID group (3.7%; 19/324). The reviewer assessed the attributability of the adverse event to study drug, taking into account the patient's past medical history, the infection being treated, the temporal association of the event to initiation of the medication, and resolution of the event with discontinuation of the medication. In almost all instances, the reviewer's assessment (related or not related) corresponded with the investigator's assessment (possible/probable or unlikely/not related). The number of possible or probable events based on the investigator's assessment is 16/517 (3.1%) for Cipro XR and 12/518 (2.3%) for Cipro BID, which are considered similar.

TABLE 54A
Permanent Discontinuation of Study Medication Due to Adverse Event(s)
Cipro XR Treatment Group (N=28)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	Adverse Event(s) Leading to D/C	Study Drug Start Date/ End Date	Date of Onset of AE	Duration (Days)	Serious Adverse Event Criteria?	Relationship [a]
4001/F/79/cUTI	Urosepsis	8/1/01 – 8/2/01	8/3/01	6	Yes (hospitalization)	Not related
15006/M/20/cUTI	Bradycardia Dizziness Double Vision	10/10/01 – 10/11/01	10/11/01 10/11/01 10/11/01	2 2 2	No No No	Possible Possible Possible
18015/F/19/AUP	Gonorrhea	10/13/01 – 10/15/01	10/15/01	Unknown	No	Not related
29131/F/58/cUTI	Vomiting	5/1/02 – 5/1/02	5/1/02	1	No	Unlikely
29148/F/53/AUP	Bacteremia	6/28/01 – 6/29/01	6/28/01	2	Yes (hospitalization)	Not Related
48010/F/83/cUTI	Increased Diarrhea	9/18/01 – 9/22/01	9/18/01	2	No	Possible
41032/M/71/cUTI	Hypotension	11/16/01 – 11/17/01	11/17/01	1	Yes (hospitalization)	Unlikely
42047/F/42/cUTI	Stomach cramps Vomiting Chills	4/3/02 – 4/13/02	4/10/02 4/10/02 4/10/02	5 4 4	No No No	Possible Possible Unlikely
45013/F/78/cUTI	Lightheadedness Dizziness	9/28/01 – 9/29/01	 9/29/01 9/29/01	2 2	No No	Possible Possible
45039/F/67/cUTI	Stomach upset	2/26/02 – 3/1/02	2/26/02	4	No	Possible
48010/F/83/cUTI	Constipation	9/18/01 – 9/22/01	9/18/01	8	No	Possible
49002/F/83/cUTI	Upset Stomach	5/17/01 – 5/19/01	5/19/01	2	No	Probable
49010/F/72/cUTI	Faint Feeling	7/23/01 – 7/26/01	7/26/01	Unresolved	No	Possible
49014/F/90/cUTI	Elevated BUN, creatinine, uric acid, and amylase	8/8/01 – 8/10/01	8/8/01	Unresolved	No	Not related
50002/F/63/cUTI	Possible Sepsis	5/14/01 – 5/15/01	5/16/01	Unresolved	Yes (hospitalization)	Not related
50007/M/74/cUTI	Worsening urinary retention	10/9/01 – 10/16/01	10/16/01	Unresolved	No	Not related
62020/F/19/AUP	Worsening of vomiting	6/18/02 – 6/19/02	6/19/02	2	No	Possible
73035/F/32/cUTI	Headaches Lightheadedness Dizziness	1/25/02 – 1/29/02	1/25/02	6	No	Not related
73036/M/84/cUTI	Diarrhea Diverticulitis Stomach bloating Dizziness Lightheadedness Weakness Nightmares Worsening depression	2/7/02 – 2/10/02	2/9/02 2/18/02 2/9/02 2/9/02 2/9/02 2/9/02 2/9/02 2/9/02	30 3 5 5 27 27 3 1	No Yes (hosp) No No No No No No	Not related Not related Not related Not related Possible Possible Probable Possible
77003/F/69/AUP	Fatigue	11/2/01 – 11/10/01	11/8/01	3	No	Probable
77011/F/84/cUTI	Worsening malaise	4/4/02 – 4/8/02	4/9/02	73	No	Possible

Patient ID/Gender/ Age/Subgroup	Adverse Event(s) Leading to D/C	Study Drug Start Date/ End Date	Date of Onset of AE	Duration (Days)	Serious Adverse Event Criteria?	Relationship [a]
82019/F/22/	Nausea Vomiting	11/28/01 – 12/1/01	11/29/01 11/29/01	3 3	No No	Probable Probable
101002/M/90/cUTI	Headache Vertigo Nausea	3/6/02 – 3/7/02	3/7/02 3/7/02 3/7/02	2 2 2	No No No	Probable Probable Probable
101003/M/87/cUTI	Dizziness	3/6/02 – 3/8/02	3/8/02	Unresolved	No	Possible
137003/F/49/cUTI	Worsened kidney stones	4/29/02 – 5/1/02	5/1/02	1	No	Not related
211001/M/59/cUTI	Hematuria	1/30/02 – 2/4/02	1/31/02	Unresolved	No	Not related
211003/M/66/cUTI	Laryngeal tumor	2/11/02 – 2/12/02	2/12/02	Unresolved	Yes (hospitalization)	Not related
213001/M/56/AUP	Headache	1/16/02 – 1/20/02	1/19/02	2	No	Probable

D/C=discontinuation; M=male; F=female
[a] Relationship as per the Investigator

TABLE 54B
Permanent Discontinuation of Study Medication Due to Adverse Event(s)
Cipro BID Treatment Group (N=19)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	Adverse Event(s) Leading to D/C	Study Drug Start Date/ End Date	Date of Onset of AE	Duration (Days)	Serious Adverse Event Criteria?	Relationship [a]
6027/M/71/cUTI	Vomiting	5/31/02 – 6/8/02	6/4/02	7	No	Possible
18004/M/30/AUP	Elevated AST Elevated ALT	8/24/01 – 8/30/01	8/27/01 8/27/01	12 12	No No	Possible Possible
19016/F/57/cUTI	Diarrhea	5/21/02 – 5/23/02	5/22/02	2	No	Probable
20006/F/21/cUTI	Nausea	8/30/01 – 9/1/01	8/30/01	3	No	Possible
49012/F/59/cUTI	Elevated LFTs	7/27/01 – 8/1/01	7/30/01	Unresolved	No	Probable
49016/F/75/cUTI	Headache	8/10/01 – 8/10/01	8/10/01	2	No	Possible
59019/M/21/cUTI	Abdominal cramping	1/17/02 – 1/22/02	1/18/02	Unresolved	No	Probable
59026/F/79/cUTI	Nausea Diarrhea	2/14/02 – 2/18/02	2/18/02 2/18/02	2 1	No	Possible Possible
62006/F/47/AUP	Itching	10/13/01 – 10/23/01	10/22/01	5	No	Probable
68004/F/54/cUTI	Worsening vaginal yeast infection	10/31/01 – 11/5/01	10/31/01	Unresolved	No	Not related
73037/M/82/cUTI	Musculoskeletal chest pain	2/7/02 – 2/8/02	2/8/02	3	No	Not related
74015/M/66/cUTI	Elevated LFTs	6/14/02 – 6/19/02	6/17/02	Unresolved	No	Possible
89001/F/84/cUTI	Elevated LFTs	11/13/01 – 11/19/01	11/16/01	37	No	Probable
90014/M/93/cUTI	Chest Pain	8/24/01 – 8/26/01	9/14/01	2	Yes (hosp)	Not related
90077/M/91/cUTI	Worsening dehydration	11/2/01 – 11/9/01	11/6/01	14	No	Unlikely
118054/F/18/AUP	Persistent tachycardia Persistent hypotension	5/2/02 –5/2/02	2/2/02 5/2/02	16 16	Yes (hosp) Yes (hosp)	Not related Not related
125001/F/69/cUTI	Worsening dyspnea (intermittent) Leg weakness Increased anxiety	3/18/02 – 3/20/02	3/19/02 3/19/02 3/19/02	2 2 2	No No No	Not related Not related Not related
142007/F/77/cUTI	Muscle pain right arm Muscle pain left arm	4/12/02 – 4/17/02	4/12/02 4/12/02	10 29	No No	Unlikely Unlikely
213006/M/41/AUP	Vomiting	4/17/02 – 4/17/02	4/18/02	2	No	Possible

D/C=discontinuation; M=male; F=female
[a] Relationship as per the Investigator

F. Deaths

Three patients in the Cipro XR group and one patient in the Cipro BID group died during the study period or during the follow-up period as shown in Table 55. All four patients had an underlying diagnosis of cUTI with one underlying condition (indwelling urinary catheter, 100 mL residual urine after voiding, or urinary retention due to benign prostatic hypertrophy). In the Cipro XR group, one of the deaths occurred 35 days after the end of study drug treatment, another occurred

during treatment, and in the third case the date of the last dose was unknown. The patient death in the Cipro BID group occurred 97 days after the end of the treatment. In all cases, the serious adverse event resulting in death was judged by the investigator to be unlikely or not related to study drug therapy, and the cause of death was reported as a concomitant condition.

TABLE 55
Summary of Patient Deaths

Treatment Group	Patient Number	Sex/Age (yr)	Day of Death Relative to		Event with Outcome of Death	Cause of Death
			First Dose	Last Dose		
Cipro XR	49015	M/95	17	unknown	Acute renal failure	Renal failure
Cipro XR	52008	F/89	43	35	Respiratory failure	Respiratory failure
Cipro XR	52012	M/76	8	0	Worsening of congestive heart failure (CHF)	Sudden death probably due to worsening of CHF
Cipro BID	73037	M/82	99	97	Left renal cancer with metastasis	Renal cell carcinoma

A short narrative of each patient who died is included below:

Patient 49015
This 95-year-old Caucasian man was enrolled for the treatment of cUTI with an indwelling urinary catheter. His medical history consisted of: hypertension, angina pectoris, constipation, back pain, seizure, prostate cancer, transurethral resection of the prostate, urinary retention, bladder outlet obstruction, hot flashes, indwelling urinary catheter, arteriosclerotic cardiovascular disease, and cerebrovascular accident. Concomitant medications included Lupron (leuprolide), Dilantin (phenytoin), enalapril, Vioxx (rofecoxib), Ditropan XL (oxybutynin), nitroglycerin, Darvocet-N (acetaminophen and propoxyphene), Lasix (furosemide), albuterol, Atrovent (ipratropium bromide), and morphine sulfate.

Ten days after his initial dose of study drug therapy, he was hospitalized with severe hematuria and acute renal failure. His creatinine values were 1 mg/dL at pretreatment (normal 0.5 - 1.6 mg/dL) and 1.2 mg/dL during treatment. His BUN values were 24 mg/dL at pretreatment (normal 4 - 34 mg/dL) and 25 mg/dL during treatment. Values for these two laboratory tests were unknown at the time of death. No treatment was reported for acute renal failure. He also had pulmonary edema, which was treated with Lasix (furosemide), and shortness of breath, which was treated with albuterol and Atrovent (ipratropium bromide).

Other events reported over the next 6 days were wheezing, bilateral ureteral obstruction, left atrial enlargement, right ventricular hypertrophy, bilateral hydronephrosis, bilateral renal cysts, swollen and discolored left hand, cardiomegaly, and anemia, (hemoglobin on Day 1 was 11.2 g/dL; 4 days later it was 10.7 g/dL [normal range is 12.5-17 g/dL]). No action was taken for these events, all of which remained unchanged except the acute renal failure, which resulted in his death on 7 days following hospitalization.

The investigator found it unlikely there was any relationship between the study drug and events of hematuria, shortness of breath, renal failure, pulmonaryedema, hydronephrosis, renal cysts, anemia, and wheezing. The swollen and discolored hand, cardiomegaly, atrial enlargement,ventricular hypertrophy, and ureteral obstruction were all considered unrelated to the study drug. The patient died 17 days after the start of study drug. It could not be determined when the patient took his last dose. Death was reportedly due to acute renal failure. The investigator found it unlikely there was any relationship between the study drug and the patient's death.

Patient 52008

This 89-year-old Caucasian woman was enrolled for the treatment of a cUTI with an indwelling urinary catheter. Her medical history consisted of hypertension, degenerative joint disease, diverticulosis, congestive heart failure, gastroesophageal reflux disease, angina pectoris, arteriosclerotic cardiovascular disease, depression, organic brain syndrome, post-menopausal, hysterectomy, and constipation. Concomitant medications included Lasix (furosemide), Norvasc (amlodipine), Lopressor (metoprolol), aspirin, Celexa (citalopram), Vioxx (rofecoxib), Surfak (docusate calcium), Isordil (isosorbide), Prevacid (lansoprazole), and Duragesic (fentanyl) patch. Thirty-four days after her last dose of study drug, she experienced respiratory failure due to congestive heart failure and general debilitation. Since she was on "do not resuscitate" orders by her family, the only treatment she received was palliative and she died of respiratory failure one day later. Her respiratory failure was considered not related to study drug.

Patient 52012

This 76-year-old Caucasian man was enrolled for the treatment of a cUTI with 100 mL of residual urine after voiding. His medical history consisted of myocardial infarction, congestive heart failure, atrial fibrillation, coronary artery disease, aortic stenosis, cardiomyopathy, COPD, respiratory failure, cardiac shock, pacemaker, coronary artery bypass surgery, prosthetic aortic valve, transurethral resection, bladder tumor, torn left rotator cuff repair, hyperglycemia, left bundle branch block, coronary stents, malfunction of prosthetic aortic valve and angina pectoris. Concomitant medications included Coumadin (warfarin), Lasix (furosemide), Coreg (carvedilol), Lanoxin (digoxin), aspirin, Cordarone (amiodarone) and Combivent inhaler (ipratropium/albuterol). On the 5th day of the study, his congestive heart failure worsened and he received remedial treatment with Lasix. He died 3 days later (8 days after beginning study drug therapy). Although the death certificate listed the cause of his death as "natural causes", the investigator believed his congestive heart failure was the actual cause of his death. The patient took his last dose of study medication approximately 6 p.m. on (b) (6) The patient went to bed at approximately 10 p.m., and at about 11 p.m. the patient's spouse noted that he was non-responsive and called an ambulance. The patient was declared dead at 12:40 a.m. on (b) (6) The investigator considered the event unrelated to the study drug.

Patient 73037

This 82-year-old Caucasian man was enrolled for treatment of a cUTI secondary to urinary retention due to BPH. His medical history consisted of shingles,

bilateral lens implant, bilateral laser eye surgery, BPH, hepatitis A, hypercholesterolemia, hypertension, and bilateral cataracts. His concomitant medications included Lipitor (atrovastatin), aspirin, Metamucil (psyllium), droperidol, potassium chloride, Dulcolax (bisacodyl), propofol, fentanyl, sevoflurane, Versed (midazolam), Zemuron (rocuronium), Robinul (glycopyrrolate), and neostigmine. This patient entered the study with blood in his urine secondary to the complicated urinary tract infection under study. The patient's pre-therapy LDH value was 285 U/L (normal range: 53 – 234 U/L); however, this was considered "not clinically significant" by the investigator. A repeat LDH value on Day 5 was still 285 U/L. On the 2nd day of study drug therapy, he developed musculoskeletal chest pain and the study drug was permanently discontinued. The following day, he had worsening of blood in his urine; no action was taken for this event. Both events resolved the next day and neither were considered related to study drug. The patient was given Septra DS (trimethoprim/sulfamethoxazole) as alternative therapy the day after study drug was discontinued to complete the course of therapy for his UTI. The 3rd day after the last dose of study drug, he was diagnosed with left renal cancer with metastasis and was hospitalized 5 days later to undergo left radical nephrectomy and periaortic lymphadenopathy. He did well following surgery and was discharged from the hospital two days later. The patient died 97 days following the completion of study drug therapy. The cause of death was metastatic renal cell carcinoma and it was not considered to be related to study drug.

G. Non-fatal Serious Adverse Events

Five percent (5%) of patients in both treatment groups experienced non-fatal serious adverse events (SAEs) (28/517 and 24/518, respectively). A summary of the non-fatal SAEs are shown in Tables 56A and 56B.

Reviewer's Comment: Tables 56A and 56B were created by the reviewer.

TABLE 56A
Listing of Patients with Non-Fatal Serious Adverse Events (SAEs)
Cipro XR Treatment Group (N=28)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration of SAE (Days)	SAE Criteria	Relationship [a]
4001/F/79/cUTI	Urosepsis	8/1/01 – 8/2/01	(b) (6)	7	Hospitalization	Not related
6026/M/78/cUTI	Hemoptysis Transient Hypotension Pneumonia	3/22/02 – 4/3/02	(b) (6)	8 1 8	Hospitalization Hospitalization Hospitalization	Not related Not related Not related
12005/M/68/cUTI	Unstable angina	2/27/02 – 3/12/02	(b) (6)	4	Hospitalization	Not related
13001/F/36/AUP	Cellulitis, right hand	5/21/01 – 6/3/01	(b) (6)	2	Hospitalization	Not related
15014/F/19/cUTI	Sickle cell crisis Sickle cell crisis	1/21/02 – 1/28/02	(b) (6)	5 2	Hospitalization Hospitalization	Not related Not related
27010/M/81/cUTI	Worsening Hypertension	2/5/02 – 2/14/02	(b) (6)	3	Hospitalization	Not related
29148/F/53/AUP	Bacteremia	6/28/02 – 6/29/02	(b) (6)	2	Hospitalization	Not related
41031/M/77/cUTI	Elective Transuretheral Prostatic Resection	11/16/01 – 11/29/01	(b) (6)	1	Hospitalization	Not related
41032/M/71/cUTI	Hypotension	11/16/01 – 11/17/01	(b) (6)	1	Hospitalization	Unlikely
42029/M/91/cUTI	Blood clot in Foley catheter	12/07/01 – 12/20/01	(b) (6)	2	Hospitalization	Not related
42056/F/53/cUTI	Recurrent Pericardial Effusion	6/7/02 – 6/20/02	(b) (6)	5	Hospitalization	Not related
45022/M/56/cUTI	Transitional cell carcinoma of bladder	11/16/02 - unknown	(b) (6)	Unresolved	Life-threatening medical event	Not related
49015/M/95/cUTI	Hematuria Acute Renal Failure	(b) (6) unknown	(b) (6)	Unresolved 7	Hospitalization Hospitalization, Death	Unlikely Unlikely
50002/F/63/cUTI	Possible sepsis	5/14/01 – 5/15/01	(b) (6)	Unresolved	Hospitalization	Not related
52004/F/81/cUTI	Rectal bleeding Worsening of hemorrhoids	10/11/01 – 10/17/01	(b) (6)	9 9	Hospitalization Hospitalization	Not related Not related
52008/F/89/cUTI	Respiratory Failure (due to congestive heart failure)	(b) (6)	(b) (6)	2	Death	Not related
52012/M/76/cUTI	Worsening of congestive heart failure	(b) (6)	(b) (6)	4	Death	Not related
53024/F/54/cUTI	Unresponsiveness Hypoventilation	1/8/02 – 1/22/02	(b) (6)	2 2	Hospitalization Hospitalization	Not related Not related
53026/F/62/cUTI	Exacerbation of systemic lupus erythematosus	1/9/02 – 1/25/02	(b) (6)	5	Hospitalization	Not related
59014/F/74/cUTI	Exacerbation of congestive heart failure	1/4/02 –1/4/02	(b) (6)	4	Hospitalization	Not related
63001/F/55/cUTI	Recurrent UTI	4/19/01 – 5/2/01	(b) (6)	4	Hospitalization	Not related
63016/M/41/cUTI	Dehydration	9/17/01 – 9/30/01	(b) (6)	3	Hospitalization	Unlikely
73036/M/84/cUTI	Diverticulitis	2/7/02 – 2/10/02	(b) (6)	3	Hospitalization	Not related

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration of SAE (Days)	SAE Criteria	Relationship [a]
74012/M/52/AUP	Right renal carcinoma Calcified sclerotic granuloma in lungs	3/18/02 – 3/31/02	(b) (6)	1 1	Hospitalization Hospitalization	Not related Not related
97002/M/78/cUTI	Chest pains	8/7/01 – 8/18/01	(b) (6)	2	Hospitalization	Unlikely
102014/F/73/cUTI	Colo-vesical fistula Diverticulosis Colonic resection Surface ulceration of colon	2/20/02 – 3/1/02	(b) (6)	2 Unresolved 1 1	Hospitalization Hospitalization Hospitalization Hospitalization	Not related Not related Not related Not related
148007/F/77/cUTI	Breast cancer Abdominal pain	4/18/02 – 5/1/02	(b) (6)	Unresolved 9	Hospitalization Hospitalization	Not related Not related
211003/M/66/cUTI	Laryngeal tumor	2/11/02 – 2/12/02	(b) (6)	Unresolved	Hospitalization	Not related

[a] Relationship as per the Investigator.

Reviewer's Comment: Among the three patients in the Cipro XR treatment group for whom a serious adverse event of sepsis was reported, 2 (4001 and 50002) had negative blood culture results and one (29148) had positive blood culture results for E. coli. Repeat blood culture results on the following day for this latter patient were negative, and furthermore, although study drug was discontinued, the alternative antimicrobial administered was ciprofloxacin. One (73007) of the two patients in the Cipro BID treatment group had a positive pretreatment blood culture result for E. coli, continued treatment with Cipro BID, and the event resolved. The other patient (74015) with reported sepsis in the Cipro BID group developed presumed septicemia while on alternative antimicrobial therapy (cinoxacin) and no blood culture specimens were obtained.

Of the two patients in the Cipro XR treatment group with a reported serious adverse event of hypotension, one (6026) had transient hypotension detected on hospital admission for other adverse events and the other (41032) was receiving triple-drug antihypertensive therapy. In the former case, study drug therapy was not discontinued; in the latter case, study drug therapy was discontinued but alternative therapy was instituted with commercially available ciprofloxacin.

TABLE 56B
Listing of Patients with Non-Fatal Serious Adverse Events
Cipro BID Treatment Group (N=24)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration (Days)	SAE Criteria	Relationship [a]
17004/F/71/cUTI	Right hip arthroplasty	8/7/01 – 8/21/01	(b) (6)	10	Hospitalization	Not related
19010/M/63/AUP	Lung surgery	9/10/01 – 9/16/01	(b) (6)	6	Hospitalization	Not related
25011/F/69/cUTI	Rectal bleeding Rectal polyps	8/27/01 – 9/9/01	(b) (6)	4 1	Hospitalization Hospitalization	Not related Not related
40003/M/74/cUTI	Acute lymphocytic leukemia	8/10/01 – 8/23/01	(b) (6)	Unresolved	Life-threatening event	Not related
41018/M/68/cUTI	Transurethral prostatectomy	10/12/01 – 10/18/01	(b) (6)	2	Hospitalization	Not related
45036/F/83/cUTI	Worsening of angina Stenosis of right coronary artery Worsening of coronary artery disease	2/8/02 – 2/14/02	(b) (6)	7 7 7	Hospitalization Hospitalization Hospitalization	Not related Not related Not related
52006/F/78/cUTI	Acute renal failure	10/17/01 – 10/22/01	(b) (6)	5	Hospitalization	Not related
53021/M/83/cUTI	Urinary bladder stones Adenocarcinoma of the bladder	10/30/01 – 11/13/01	(b) (6)	10 Unresolved	Hospitalization Hospitalization	Not related Not related
59005/M/64/cUTI	Musculoskeletal back spasms	8/6/01 – 8/19/01	(b) (6)	2	Hospitalization	Not related
59010/F/69/cUTI	Myocardial infarction Angina pectoris	11/2/01 – 11/15/01	(b) (6)	4 Unresolved	Hospitalization Hospitalization	Not related Not related
73007/F/73/AUP	Urosepsis	4/30/01 – 5/13/01	(b) (6)	19	Prolongation of Hospitalization	Not related
73009/F/72/cUTI	Right coronary artery occlusion	5/7/01 – 5/7/01	(b) (6)	2	Hospitalization	Not related
73019/M/88/cUTI	Coronary artery disease Excessive post-op bleeding Bronchospasm	7/20/01 – 7/26/01	(b) (6)	Unresolved 1 1	Hospitalization Hospitalization Hospitalization	Not related Not related Not related
73037/M/82/cUTI	Left renal cancer with metastasis	(b) (6)	(b) (6)	Unresolved	Death	Not related
74015/M/66/cUTI	Elevated temperature Septicemia	6/14/02 – 6/19/02	(b) (6)	6 6	Hospitalization Hospitalization	Not related Not related
82011/F/72/AUP	Abdominal pain	10/9/01 – 10/9/01	(b) (6)	2	Hospitalization	Not related
82025/F/34/AUP	Perforated duodenum secondary to duodenal ulcer repair	12/19/01 – 12/29/01	(b) (6)	8	Hospitalization	Unlikely
82028/F/42/AUP	Deep vein thrombosis	1/26/02 – 2/6/02	(b) (6)	2	Hospitalization	Not related
90014/M/93/cUTI	Chest pain	8/24/01 – 8/26/01	(b) (6)	2	Hospitalization	Not related
95017/F/71/cUTI	Vomiting	9/25/01 – 10/8/01	(b) (6)	7	Hospitalization	Not related
118054/F/18/AUP	Persistent tachycardia Persistent hypotension	5/2/02 – 5/2/02	(b) (6)	15 15	Hospitalization Hospitalization	Not related Not related
123003/M/67/cUTI	Bleeding internal hemorhoid	3/15/02 – 3/29/02	(b) (6)	3	Hospitalization	Not related

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration (Days)	SAE Criteria	Relationship [a]
142015/M/84/cUTI	Pnemonia	5/15/02 – 5/28/02	(b) (6)	5	Hospitalization	Unlikely

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration (Days)	SAE Criteria	Relationship [a]
149006/M/48/cUTI	Worsening of kidney pain	(b) (6) – unknown	(b) (6)	1	Significant disability/ incapacity (outpatient surgical intervention)	Not related

[a] Relationship as per the Investigator.

Reviewer's Comment: The patient (118054) in the Cipro BID group for whom hypotension was reported as a serious adverse event (SAE) had a history of hypotension. Hypotension (blood pressure of 92/52 mmHg) was reported as a SAE on the first day of study drug treatment, study drug was prematurely discontinued, and alternative therapy included a dose of ceftriaxone followed by ciprofloxacin. The hypotension resolved.

H. Pregnancy

One pregnancy was reported during the study in a patient treated with Cipro BID.

Patient 31042
This 19-year-old woman was enrolled for the treatment of AUP. Concomitant medication included Ortho-Cyclen (norgestimate/ethinyl estradiol). On the 11th day of the study she experienced nausea and lightheadedness for which no action was taken. Twenty-three (23) days after her final dose of study medication, she discovered she was pregnant and elected to terminate the pregnancy 15 days later; a telephone follow-up 1 month later revealed no sequelae to the procedure. All adverse events resolved. The nausea and lightheadedness were considered possibly related to the study drug; the unintended pregnancy was considered not related.

I. Evaluation of Laboratory Parameters

Laboratory variables that showed at least a 2% incidence rate of abnormalities in at least one of the treatment groups are shown in Table 57. The incidence of abnormal laboratory test results is low and generally consistent between the two treatment groups.

TABLE 57
Incidence Rates [a] of Laboratory Abnormalities Occurring in at least 2% of Patients in Either Treatment Group
Patients Valid for Safety

Laboratory Variable[b]	Cipro XR	Cipro BID
High		
WBC	14/365 (4%)	23/356 (6%)
Neutrophils (segs) absolute count	28/358 (8%)	20/336 (6%)
Lymphocytes absolute count	17/448 (4%)	10/452 (2%)
Eosinophils absolute count	8/464 (2%)	4/465 (<1%)
Platelets	31/421 (7%)	34/426 (8%)
PT[c]	4/ 55 (7%)	3/ 55 (5%)
Glucose, fed, unspecified[d]	0/ 52 (0%)	4/ 48 (8%)
Uric acid	23/436 (5%)	29/442 (7%)
Creatinine	22/435 (5%)	19/443 (4%)
BUN	17/442 (4%)	19/456 (4%)
SGOT/AST	22/434 (5%)	27/424 (6%)
SGPT/ALT	33/432 (8%)	27/426 (6%)
GGT	13/416 (3%)	16/400 (4%)
LDH	12/434 (3%)	17/441 (4%)
Alkaline phosphatase	7/450 (2%)	12/455 (3%)
Bilirubin, total	6/458 (1%)	8/469 (2%)
Amylase	26/411 (6%)	39/414 (9%)
Specific gravity	16/460 (3%)	11/468 (2%)
Low		
Hematocrit	42/412 (10%)	25/419 (6%)
Hemoglobin	41/392 (10%)	27/408 (7%)
WBC	10/464 (2%)	11/467 (2%)
Neutrophils (segs) absolute count	12/464 (3%)	14/469 (3%)
Lymphocytes absolute count	13/447 (3%)	10/449 (2%)
Bilirubin, total	30/445 (7%)	30/462 (6%)
Specific gravity	52/440 (12%)	53/460 (12%)

[a] Incidence rate = Number of patients with the abnormality after pretreatment / Number of patients with readings during and after pretreatment who did not have the abnormality during pretreatment.
[b] Fasting state was not mandated.
[c] Samples for PT were obtained only from patients who were receiving concomitant therapy with Coumadin.
[d] Glucose, fed or unspecified; values for this laboratory analyte (n = 100 patients) were determined only after approval of Protocol Amendment # 6.

The incidence rates of urine abnormalities are similar between the two treatment groups. Blood was documented in urine macroscopically in about one-fifth of patients (20% in Cipro XR patients and 17% in Cipro BID patients). RBCs are seen in the urine in 14% and 17% of patients treated with Cipro XR and Cipro BID, respectively. Hematuria was reported as an adverse event in < 1% of patients in either treatment group (5 Cipro XR patients and 3 Cipro BID patients), of which only 1 case (Cipro XR, Patient 142021) was considered by the investigator to be drug related. This patient, was receiving warfarin for atrial

fibrillation and presented at study entry with moderate hematuria among other signs and symptoms of cUTI, developed gross hematuria one day after starting Cipro XR therapy. His INR the following day was 1.98. The event resolved in one day without any intervention. The patient had no other adverse events.

Changes from baseline for all laboratory variables generally are comparable between the two treatment groups. Of the 5 patients who discontinued study drug therapy prematurely due to laboratory test abnormalities (Patient 49014 in the Cipro XR group with elevated BUN and creatinine and Patients 18004, 49012, 74015 and 89001 in the Cipro BID group with increased liver function tests), four had elevations at baseline. The fifth patient, an 84 year of female (Patient 89001) in the Cipro BID group, experienced an increase in liver enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, and alkaline phosphatase) and total bilirubin during the study. The laboratory values are well within the normal range at baseline but increased from 1.5- to >10-times the upper limit of normal three days after beginning study drug. The patient did not experience jaundice, nausea or vomiting during the time of elevated tests. Study drug was discontinued and the tests all returned to baseline and are in the normal range by 18 days following the discontinuation of study drug.

Criteria used to define potentially clinically significant changes for common laboratory variables are as follows: < 75% of the lower limit of normal for hemoglobin; <100,000/mm^3 for platelets; > 0.5 mg/dL and > 1mg/dL increase from baseline for serum creatinine; ≥ 1.8 and > 3 times the upper limit of normal (ULN) for SGPT (ALT), SGOT (AST) and total bilirubin; and < 50 mg/dL for serum glucose. The highest incidence of such changes in the Cipro XR group is 2% for creatinine increase > 0.5 mg/dL from baseline, SGOT/AST, and SGPT/ALT >1.8 times ULN as shown in Table 58. In the Cipro BID group the highest incidence of clinically significant changes also is 2% for elevation of liver enzymes (SGOT/AST, and SGPT/ALT) > 1.8 and > 3 times ULN.

TABLE 58
Incidence of Clinically Significant Laboratory Abnormalities
Patients Valid for Safety

Variable	Criterion	Cipro XR		Cipro BID	
		n/n	%	n/n	%
Hemoglobin	0.75 x lower limit or less	2/479	<1	1/481	<1
Total bilirubin	≥1.8 x ULN	2/484	<1	2/491	<1
	≥3 x ULN	1/484	<1	1/493	<1
Creatinine	Increase of 0.5 mg/dL from baseline	11/486	2	6/498	1
	Increase of 1 mg/dL from baseline	3/486	1	1/498	<1
SGOT/AST	≥1.8 x ULN	8/464	2	11/467	2
	>3 x ULN	4/472	1	8/477	2
SGPT/ALT	≥1.8 x ULN	9/475	2	10/467	2
	>3 x ULN	6/479	1	10/481	2

Of the three patients with hemoglobin values <75% of the lower limit of normal, only one patient (Cipro BID, Patient 90014 had symptoms that could potentially

be associated with anemia (chest pain, malaise, and worsening of shortness of breath). However, considering the timing of adverse events, malaise is more likely to have been a consequence of indigestion and diarrhea that the patient developed at the same time. This patient also had a history of anemia and shortness of breath as well as multiple cardiovascular conditions, including aortic stenosis, congestive heart failure, angina pectoris, arteriosclerosis, hypertension, to which the other two adverse events could have been related.

Reviewer's Comment: Two patients had clinically significant increases (≥3 x ULN; ULN = 1.2 mg/dL) in total bilirubin after receiving study drug. Patient 95009 was a 57-year-old Caucasian female randomized to Cipro BID for cUTI. Her pre-test total bilirubin was 0.7 mg/dL, which increased to 6 mg/dL at the TOC visit. However at the post-therapy visit the value was decreased to 0.2 mg/dL. There was no concurrent increase in AST or ALT with the rise in total bilirubin at the TOC visit.

Patient 124004 was an 82-year-old Caucasian female randomized to Cipro XR for cUTI. Her pre-test total bilirubin was 0.6 mg/dL. At the during therapy visit, the value increased to 1.1 mg/dL, and was noted to be 4.8 mg/dL at the TOC visit. An additional visit, scheduled more than one month after the end of therapy, showed a reduction in total bilirubin to 1.3 mg/dL. The values of AST and ALT remained within normal limits throughout.

Although there are more patients in the Cipro XR group whose creatinine levels rose from baseline by more than 0.5 mg/dL (11 versus 6 patients), comparable numbers of patients in both treatment groups had a change in creatinine levels from baseline greater than 1 mg/dL (3 versus 1 patient). For only one of these patients (Cipro XR, Patient 82019) the increase in creatinine level (from 0.8 mg/dL at baseline to 2.8 and 3.0 mg/dL on the third and fourth days of study drug therapy, respectively) was reported as an adverse event and the patient developed possibly related symptoms of nausea, vomiting, and tingling in extremities. The event resolved in about 1 month (creatinine levels were 2.1, 1.7, and 0.9 mg/dL on the second, fifth, and thirty-fourth post-treatment days, respectively). Only 1 patient (Cipro XR, 49014) discontinued study drug due to abnormal kidney function, which was detected at baseline (creatinine 2.3 mg/dL pre-treatment; 2.5 mg/dL on Day 3; 2.5 mg/dL at +7 days post-treatment; and BUN 91 mg/dL pretreatment; 96 mg/dL on Day 3; 99 mg/dL at +7 days post-treatment).

In the two treatment groups, the incidence of clinically significant (>1.8 x ULN) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that were >3 x ULN, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients (<1%) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. For one patient (31035) the liver enzyme levels were increased less than 1.8x ULN and were thought to be possibly related to study drug. In the other patient (25008) the liver enzyme levels were 3x ULN and 4.8x ULN for SGOT and SGPT, respectively, and not believed to be related to study drug. In both cases, the events resolved and did not require discontinuation of study drug.

Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one patient (89001) of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline. This patient had diabetes mellitus and was receiving concomitant therapy with oral antidiabetic agents and insulin. On Day 4, her SGOT and SGPT levels increased to >10 x ULN, GGT to >5 x ULN, LDH to >2 x ULN, alkaline phosphatase to 1.4 x ULN, and total bilirubin to 3 x ULN. Values returned toward baseline levels following discontinuation of study drug, and the investigator judged the event of elevated liver function tests to be probably study related.

J. Vital signs, physical findings, and other observations related to safety

All vital signs are comparable between the two treatment groups throughout the study (i.e., pre-therapy, test of cure, and follow-up). The mean change from pre-therapy at the TOC visit and at the late follow-up visit for all vital signs variables generally are minimal (data not shown).

XI. Safety Results for Special Populations

A. Age

Adverse events occurring in at least 2% of patients in any age group (< 65 years, 65 to 74 years and ≥ 75 years) are summarized in Table 59.

The overall incidence rates of adverse events are similar across age groups (< 65 years, 65-74 years, and ≥ 75 years) in patients within each treatment group. For both the Cipro XR and Cipro BID group, patients aged 65-74 years experienced nausea less frequently than those younger or older. More patients younger than 65 years of age in the Cipro XR group reported vomiting [4% (12/271)] than did patients in the same age category treated with Cipro BID [<1% (2/255)]. The incidence of dizziness in patients 75 years of age or older is slightly higher in the Cipro XR group [4% (6/149)] as compared to the Cipro BID group [1% (2/159)]. The incidence rates of other adverse events for both treatment groups across age groups are similar.

TABLE 59
Incidence Rates of Adverse Events by Age
Occurring in at least 2% of Any Age Group by Treatment Group
Patients Valid for Safety

Adverse Event	n (%)					
	<65 Years		65-74 Years		≥ 75 Years	
	Cipro XR N = 271	Cipro BID N = 255	Cipro XR N = 97	Cipro BID N = 104	Cipro XR N = 149	Cipro BID N = 159
Any Body System						
Any Event	85 (31)	79 (31)	29 (30)	36 (35)	51 (34)	50 (31)
Body as a Whole						
Any Event	31 (11)	32 (13)	5 (5)	10 (10)	18 (12)	16 (10)
Headache	12 (4)	14 (5)	0 (0)	4 (4)	5 (3)	7 (4)
Abdominal pain	2 (<1)	0 (0)	1 (1)	0 (0)	3 (2)	0 (0)
Back pain	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	3 (2)
Fever	0 (0)	3 (1)	0 (0)	2 (2)	0 (0)	1 (<1)
Asthenia	0 (0)	0 (0)	3 (3)	0 (0)	1 (<1)	0 (0)
Sepsis	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Cardiovascular System						
Any Event	4 (1)	6 (2)	9 (9)	3 (3)	7 (5)	7 (4)
Peripheral edema	1 (<1)	0 (0)	2 (2)	0 (0)	2 (1)	0 (0)
Hypotension	0 (0)	0 (0)	2 (2)	0 (0)	1 (<1)	0 (0)
Digestive System						
Any Event	41 (15)	32 (13)	7 (7)	16 (15)	23 (15)	19 (12)
Nausea	14 (5)	11 (4)	1 (1)	2 (2)	9 (6)	10 (6)
Diarrhea	8 (3)	6 (2)	0 (0)	1 (<1)	7 (5)	4 (3)
Vomiting	12 (4)	2 (<1)	1 (1)	3 (3)	1 (<1)	3 (2)
Dyspepsia	5 (2)	2 (<1)	3 (3)	1 (<1)	1 (<1)	3 (2)
Constipation	2 (<1)	3 (1)	0 (0)	3 (3)	3 (2)	3 (2)
LFTs abnormal	0 (0)	3 (1)	0 (0)	2 (2)	0 (0)	2 (1)
Rectal hemorrhage	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
GI neoplasia	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Nervous System						
Any Event	14 (5)	8 (3)	4 (4)	8 (8)	12 (8)	4 (3)
Dizziness	6 (2)	3 (1)	4 (4)	5 (5)	6 (4)	2 (1)
Anxiety	0 (0)	1 (<1)	0 (0)	2 (2)	0 (0)	0 (0)
Respiratory System						
Any Event	9 (3)	14 (5)	6 (6)	3 (3)	4 (3)	4 (3)
Pharyngitis	2 (<1)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Skin and Appendages						
Any Event	7 (3)	4 (2)	1 (1)	0 (0)	2 (1)	6 (4)
Pruritus	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	3 (2)

Adverse Event	n (%)					
	<65 Years		65-74 Years		≥ 75 Years	
	Cipro XR N = 271	Cipro BID N = 255	Cipro XR N = 97	Cipro BID N = 104	Cipro XR N = 149	Cipro BID N = 159
Urogenital System						
Any Event	20 (7)	20 (8)	5 (5)	5 (5)	14 (9)	9 (6)
Vaginal moniliasis	7 (3)	7 (3)	2 (2)	0 (0)	1 (<1)	1 (<1)
Urinary retention	2 (<1)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Hematuria	1 (<1)	0 (0)	0 (0)	0 (0)	4 (3)	0 (0)

Note: Incidence rate = Number of events / Number of patients, where number of events is the number of patients reporting the event with a start date during or after treatment

Reviewer's Comment: The differences seen in adverse events between younger and older patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by age in product labeling.

B. Sex

Adverse events occurring in at least 2% of patients in any treatment group by sex are shown in Table 60.

Within each sex, the event rates are similar between Cipro XR and Cipro BID patients. Overall, female patients have higher event rates than male patients [34% (102/298) for females vs. 29% (102/299) for males]. Overall, female patients have higher rates of nausea and diarrhea [nausea: 6% in both Cipro XR (19/298) and Cipro BID (18/299) groups; diarrhea: 4% (11/298) in Cipro XR and 3% (8/299) in Cipro BID] than the male patients [nausea: 2% in both Cipro XR (5/219) and Cipro BID (5/219) groups; diarrhea: 2% (4/219) in Cipro XR and 1% (3/219) in Cipro BID). Of the Cipro XR treated patients more females reported vomiting [4% (12/298)] than males [<1% (2/219)].

TABLE 60
Incidence Rates of Adverse Events by Sex
Occurring in at least 2% of Patients of Either Sex
Patients Valid for Safety

Adverse Event	n (%)			
	Male		Female	
	Cipro XR N=219	Cipro BID N=219	Cipro XR N=298	Cipro BID N=299
Any Event	63 (29%)	63 (29%)	102 (34%)	102 (34%)
Headache	6 (3%)	9 (4%)	11 (4%)	16 (5%)
Back pain	2 (<1%)	1 (<1%)	2 (<1%)	5 (2%)
Abdominal pain	0 (0%)	1 (<1%)	6 (2%)	3 (1%)
Nausea	5 (2%)	5 (2%)	19 (6%)	18 (6%)
Constipation	2 (<1%)	6 (3%)	3 (1%)	3 (1%)
Vomiting	2 (<1%)	6 (3%)	12 (4%)	2 (<1%)
Diarrhea	4 (2%)	3 (1%)	11 (4%)	8 (3%)
Dyspepsia	2 (<1%)	4 (2%)	7 (2%)	2 (<1%)
LFTs abnormal	1 (<1%)	4 (2%)	1 (<1%)	3 (1%)
Dizziness	6 (3%)	4 (2%)	10 (3%)	6 (2%)
Hematuria	5 (2%)	2 (<1%)	0 (0%)	1 (<1%)
Urogenital surgery	4 (2%)	1 (<1%)	0 (0%)	0 (0%)
Vaginal moniliasis	0 (0%)	0 (0%)	10 (3%)	8 (3%)

Reviewer's Comment: The differences seen in adverse events between male and female patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by sex in product labeling.

C. Race

Adverse events occurring in at least 2% of patients in any treatment group by race (Caucasian, Hispanic, Black) is shown in Table 61. Conclusions cannot be made for patients categorized as Asian or American Indian because their numbers are too small for a meaningful comparison.

Adverse event rates generally are consistent across subgroups. The number of patients with any adverse event is comparable between the two treatments for Caucasian: 31% (129/410) for Cipro XR and 33% (138/414) for Cipro BID and Hispanic 27% (13/48) for Cipro XR and 30% (16/53) for Cipro BID patients. Black patients treated with Cipro XR have a higher incidence of adverse events [38% (21/55)] compared with Black patients treated with Cipro BID [23% (11/48)]. This is due primarily to adverse events attributed to the urogenital system: 16% (9/55) in Cipro XR-treated patients versus 8% (4/48) Cipro BID-treated patients.

Within the Cipro XR group, more Hispanic patients developed nausea, headache, or vomiting than did black or Caucasian patients. In the Cipro BID group, Hispanic patients have a higher incidence of abdominal pain than did patients of the other two racial groups. There are no other notable differences between the two treatment groups by race. Overall, there are no clinically

meaningful differences in the incidence of adverse events across the three racial sub-groups (i.e., Caucasian, Black, and Hispanic).

TABLE 61
Incidence Rates of Adverse Events by Race
Occurring in at least 2% of Patients of Any Race by Treatment Group
Patients Valid for Safety

Adverse Event	n (%)					
	Caucasian		Hispanic		Black	
	Cipro XR N = 410	Cipro BID N = 414	Cipro XR N = 48	Cipro BID N = 53	Cipro XR N = 55	Cipro BID N = 48
Any Body System						
Any Event	129 (31)	138 (33)	13 (27)	16 (30)	21 (38)	11 (23)
Body As A Whole						
Any Event	42 (10)	47 (11)	7 (15)	7 (13)	5 (9)	4 (8)
Headache	12 (3)	20 (5)	4 (8)	3 (6)	1 (2)	2 (4)
Abdominal Pain	5 (1)	1 (<1)	1 (2)	3 (6)	0 (0)	0 (0)
Back Pain	0 (0)	5 (1)	0 (0)	0 (0)	0 (0)	1 (2)
Asthenia	0 (0)	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)
Sepsis	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Chest pain	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)
Digestive System						
Any Event	58 (14)	59 (14)	8 (17)	5 (9)	5 (9)	3 (6)
Nausea	18 (4)	21 (5)	6 (13)	1 (2)	0 (0)	1 (2)
Diarrhea	14 (3)	8 (2)	0 (0)	1 (2)	1 (2)	2 (4)
Vomiting	8 (2)	6 (1)	4 (8)	1 (2)	2 (4)	1 (2)
Dyspepsia	8 (2)	5 (1)	1 (2)	0 (0)	0 (0)	1 (2)
Constipation	0 (0)	8 (2)	0 (0)	1 (2)	0 (0)	0 (0)
LFTs abnormal	0 (0)	6 (1)	0 (0)	1 (2)	0 (0)	0 (0)
Anorexia	0 (0)	3 (<1)	1 (2)	0 (0)	1 (2)	1 (2)
Heme and Lymphatic System						
Any Event	4 (<1)	3 (<1)	0 (0)	0 (0)	1 (2)	1 (2)
Anemia	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Metabolic and Nutritional System						
Any Event	7 (2)	2 (<1)	1 (2)	1 (2)	0 (0)	0 (0)
Dehydration	4 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Musculoskeletal System						
Any Event	5 (1)	10 (2)	0 (0)	2 (4)	1 (2)	0 (0)
Arthralgia	2 (<1)	2 (<1)	0 (0)	2 (4)	1 (2)	0 (0)
Myalgia	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Nervous System						
Insomnia	0 (0)	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)
Hypertonia	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Respiratory System						
Any Event	16 (4)	18 (4)	1 (2)	1 (2)	2 (4)	2 (4)
Pharyngitis	4 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)

Adverse Event	n (%)					
	Caucasian		Hispanic		Black	
	Cipro XR N = 410	Cipro BID N = 414	Cipro XR N = 48	Cipro BID N = 53	Cipro XR N = 55	Cipro BID N = 48
Rhinitis	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Dyspnea	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Cough increased	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)
Skin and Appendages						
Any Event	7 (2)	7 (2)	1 (2)	1 (2)	1 (2)	2 (4)
Pruritus	0 (0)	2 (<1)	0 (0)	1 (2)	0 (0)	1 (2)
Special Senses						
Any Event	5 (1)	3 (<1)	1 (2)	1 (2)	1 (2)	1 (2)
Special senses surgery	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Urogenital System						
Any Event	26 (6)	28 (7)	4 (8)	2 (4)	9 (16)	4 (8)
Vaginal Moniliasis	7 (2)	8 (2)	2 (4)	0 (0)	1 (2)	0 (0)
Hematuria	4 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Dysuria	2 (<1)	3 (<1)	0 (0)	1 (2)	1 (2)	0 (0)
Urinary retention	4 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Vaginitis	1 (<1)	0 (0)	1 (2)	1 (2)	1 (2)	2 (4)
Urogenital surgery	2 (<1)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)

Note: Incidence rates = Number of events / Number of patients, where number of events is the number of patients reporting the event with a start date during or after treatment
Note: Asian and American Indian races are not shown because of small numbers.

Reviewer's Comment: The differences seen in adverse events between racial subgroups treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by race in product labeling.

XII. Clinical Reviewer's Conclusions of Study 100275

A. Efficacy Conclusions

Cipro XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients and compared Cipro XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days). The primary endpoint for this trial is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in AUP and cUTI patients combined in the valid for efficacy (Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

There are several problems with the applicant's analysis of bacteriologic eradication in cUTI and AUP patients combined in the Per Protocol (PP) population.

- First, there is a difference in the treatment effect between patients with AUP and cUTI. The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%). In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the ciprofloxacin BID group (81.4%). The *P* value from the Breslow-Day test for treatment-by-infection interaction is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients. The Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients due to the significant treatment-by-infection interaction.

- Second, although not specified by the applicant, the Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. When the MITT population is examined along with reasons for exclusion from the PP population, there are significantly more patients in the Cipro XR group (40%, 136/342) than in the Cipro BID group (29%, 95/324) that had been excluded from the PP population. Exclusions from the PP population are primarily a result of premature discontinuations, which are primarily due to adverse events (2.9% versus 1.7%, respectively) and no valid test-of-cure (TOC) urine culture or lost to follow-up (7.7% versus 4.6%, respectively). A differential rate in exclusion may bias the results of any analysis using this population.

Therefore, the bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer and reported for both the MITT and PP populations. Since in the applicant's analysis random assignment of treatment was stratified by infection type, the calculation of the difference in eradication

rates between treatment groups for each stratum alone must be adjusted for multiple comparisons (i.e., 97.5% confidence intervals). The bacteriologic eradication rates and their corresponding 97.5% confidence intervals for the differences between rates (Cipro XR minus Cipro BID) for AUP and cUTI patients, at the TOC visit are given in the following table for both the MITT and PP populations.

Bacteriologic Eradication at TOC (+5 to +11 Days) in AUP and cUTI Patients

	MITT*		PP**	
	n/N (% of Patients)	[95% CI of the Difference]	n/N (% of Patients)	[95% CI of the Difference]
AUP Patients				
Cipro XR	47/71 (66.2%)	[-26.8, 6.5]	35/40 (87.5%)	[-34.8, 6.2]
Cipro BID	58/76 (76.3%)		51/52 (98.1%)	
cUTI Patients				
Cipro XR	160/271 (59.0%)	[-13.5, 5.7]	148/166 (89.2%)	[-0.7, 16.3]
Cipro BID	156/248 (62.9%)		144/177 (81.4%)	

* Patients excluded from the Modified Intent-to-Treat group are those with no causative organism at baseline and those who did not receive study drug.

** Patients excluded from the Per Protocol group are those with no causative organism(s) at baseline, no valid TOC urine culture, inclusion/exclusion criteria violation, organism resistant to study drug, protocol violation, non-compliance with dosage regimen, did not receive study drug, inadequate duration of treatment, post-therapy antibiotics, and concomitant antimicrobial therapy.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above –10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

Additional analyses were performed in an attempt to assess how Cipro XR compares to Cipro BID with respect to persistence of the baseline pathogen, and subsequent clinical response.

The applicant's definition in this study of bacteriologic eradication considers patients with new infections and superinfections to be treatment failures. In the PP population, of the 40 patients with AUP treated with Cipro XR, 35 were eradicated, 2 had persistence (1 *E. coli* and 1 *E. faecalis*), and 3 developed new infections with *E. faecalis* (2 with *E. coli* as baseline pathogen and one with *S. saprophyticus*). Of the 52 patients with AUP treated with Cipro BID, 51 were eradicated. One patient had persistence of *E. faecalis*.

The most common organism isolated from the urine of AUP patients is *E. coli*. The bacteriologic eradication rate for *E. coli* in the PP population is 97.2% (35/36) for the Cipro XR group and 100% (41/41) in the Cipro BID group.

In the PP population, of the 166 patients with cUTI treated with Cipro XR, 148 were eradicated, 8 had persistence, 5 patients developed superinfections, and 5 patients developed new infections. Of the 177 patients with cUTI treated with Cipro BID, 144 were eradicated, 16 had persistence, 3 patients developed superinfections, and 14 fourteen developed new infections.

The most common organisms isolated from the urine of cUTI patients are *E. coli*, *K. pneumoniae*, *E. faecalis*, and *P. mirabilis*. The bacteriologic eradication rates of these organisms in the PP population, in order, are 96.8% (91/94), 95.2% (20/21), 100% (17/17), and 91.6% (11/12) for the Cipro XR group. In the PP population of the Cipro BID group, the rates, in order, are 97.8% (90/92), 82.6% (19/23), 66.7% (14/21), and 100% (10/10).

Results for all the applicant's secondary variables (i.e., bacteriological response at the late follow-up visit and clinical response at the test-of-cure and late follow-up visits), in the PP population for AUP and cUTI patients separately, are summarized as follows:

- The bacteriologic eradication rates at the late follow-up visit in AUP patients are lower in the Cipro XR group (62.5%, 25/40) compared to the Cipro BID group (67.3%, 35/52). In cUTI patients, the rates are higher in the Cipro XR group (59.6%, 99/166) compared to the Cipro BID group (45.2%, 80/177). The differences between the two patient groups follows a similar trend to the results at the TOC visit.

- The clinical response at the TOC visit in AUP patients is similar for the Cipro XR and Cipro BID groups [97.5% (39/40) and 96.2% (50/52), respectively]. In cUTI patients, the response rates are slightly higher in the Cipro XR group (95.8%, 159/166) compared to the Cipro BID group (91.0%, 161/177).

- The clinical response at the late follow-up visit in AUP patients is slightly lower for the Cipro XR group (75%, 30/40) compared to Cipro BID group (80.8%, 42/52). In cUTI patients, the response rates are slightly higher in the Cipro XR group (72.3%, 120/166) compared to the Cipro BID group (61.6%, 109/177).

Differences seen, if any, in bacteriologic eradication rates between younger and older patients, males and females, and those of various races are not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on age, sex, or race.

B. Safety Conclusions

Of the 1042 patients enrolled in the study, 1035 received at least one dose of study drug and are valid for the analysis of safety (517 in the Cipro XR group and 518 in the Cipro BID group. The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups.

More patients in the Cipro XR group (28 patients or 5.4%) than in the Cipro BID group (19 patients or 3.7%) discontinued study drug due to an adverse event.

The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

The most common adverse events in both treatment groups are those occurring in the digestive system [14% (71/517) for Cipro XR and 13% (67/518) for Cipro BID]. The incidence of adverse events for each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30/517) experienced at least one adverse event involving the nervous system compared with 4% (20/518) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [<1%] versus 0 patients [0%], respectively).

Most patients in both treatment groups who experienced adverse events had events that were assessed by the investigator as mild or moderate in intensity. Adverse events that occurred in at least 2% of patients treated with Cipro XR include nausea (5%), headache (3%), diarrhea (3%), vomiting (3%), dizziness (3%), dyspepsia (2%), and vaginal moniliasis (2%). Cipro BID has a similar profile of adverse events occurring in at least 2% of patients, with a slightly higher incidence of headache (5%).

Study drug-related (possible or probable relationship) adverse events were reported in 13% (68/517) of patients in the Cipro XR group and 14% (70/518) of patients in the Cipro BID group. Those occurring in 2% or more of patients in either treatment group include headache, nausea, diarrhea, dizziness, and vaginal moniliasis.

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event assessed by the investigator as severe in intensity. The number of severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Four patient deaths were reported during the study (3 in the Cipro XR group and one in the Cipro BID group). All four patients were in the older age range (76 to 95 years), had a diagnosis of cUTI with one underlying condition, and had other concurrent medical conditions requiring concomitant medications. In all cases, the adverse event resulting in death was judged by the investigator to be of unlikely or no relationship to study drug and the FDA reviewer concurred.

Patients experiencing non-fatal serious adverse events (SAEs) is 5% in both treatment groups, (28/517 and 24/518, respectively). All SAEs reported in the Cipro XR group were judged by the investigators to be unlikely or not related to study drug.

In the two treatment groups, the incidence of clinically significant (>1.8 x ULN) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that are >3 x ULN, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients (<1%) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. In both cases, the events resolved and did not require discontinuation of study drug. Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline.

The incidence of other laboratory test abnormalities is low and comparable between the two treatment groups. Descriptive statistics of the change from baseline in laboratory test results does not reveal any trends that appear to be uniquely associated with Cipro XR treatment.

Overall, there are no clinically meaningful differences in the safety profile of either treatment on the basis of age, sex, or race.

APPENDIX 2 – ADDITIONAL TABLES FOR STUDY 100275

Table 2 is modified from the applicant's submission by the reviewer for clarity

TABLE 2
List of Investigators and Number of Patients per Treatment Arm
All Randomized (N=1042)

Site Number	Principal Investigator	Treatment Arm					
		Ciprofloxacin XR (N=521)			Ciprofloxacin BID (N=521)		
		Randomized	Valid for Safety	Per Protocol	Randomized	Valid for Safety	Per Protocol
2	Bastuba	1	1	0	1	1	0
4	Bergreen	3	3	1	2	2	1
6	Childs	10	10	5	10	10	5
12	Durden	4	4	2	4	4	1
13	Elashker	4	4	1	3	3	2
15	Foote	9	9	3	10	10	4
16	Casey	0	0	0	1	1	1
17	Garcia	4	4	1	4	4	1
18	Giordano	6	6	2	5	5	2
19	Goldfischer	9	9	2	7	7	1
20	Hellstrom	7	7	2	6	6	1
25	Klimberg	10	10	5	17	17	12
26	Knapp	6	6	3	7	7	4
27	Auerbach	5	5	1	5	5	1
29	Mullins	8	8	1	6	6	3
31	McMurray	10	10	7	11	11	4
34	Raad	0	0	0	1	1	1
35	Rafelson	0	0	0	1	1	1
36	Randall	8	6	2	9	8	4
37	Rosenberg	3	3	1	3	3	1
38	Rozas	1	1	0	1	1	0
39	Saltzstein	3	3	2	3	3	2
40	Shami	4	4	1	3	3	2
41	Sharifi	8	8	4	9	9	8
42	Siami	27	27	11	30	30	16
45	Taub	19	19	7	19	19	10
48	Wegenke	16	16	10	16	16	9
49	Young	24	24	12	23	23	9
50	Zinner	6	6	3	6	6	5
51	Fiel	1	1	1	0	0	0
52	Colan	7	7	1	6	6	1
53	Brown	15	15	7	16	16	8
54	Elliott	1	1	0	0	0	0
59	Feldman	16	16	5	16	16	4
62	McCarron	10	10	4	8	7	5
63	Mirelman	8	8	2	7	7	5
64	Moseley	7	7	4	5	5	1
66	Ott	0	0	0	1	1	0

Site Number	Principal Investigator	Treatment Arm					
		Ciprofloxacin XR (N=521)			Ciprofloxacin BID (N=521)		
		Randomized	Valid for Safety	Per Protocol	Randomized	Valid for Safety	Per Protocol
68	Schiff	6	6	1	4	4	1
70	Snyder	2	2	0	1	1	0
73	Tomera	20	20	7	22	21	7
74	Wells	8	8	2	7	7	4
75	Shockey	3	3	1	3	3	2
76	Dahdul	5	5	2	6	6	2
77	Kaminetsky	5	5	2	5	5	3
82	Talan	12	12	5	15	15	7
86	Canfield	3	3	0	2	2	2
88	Panebianco	1	1	0	1	1	0
89	Teitelbaum	0	0	0	1	1	0
90	Wolf-Klein	1	1	1	2	2	1
91	Hoffman	3	3	1	3	3	1
92	Stringer	7	7	5	6	6	4
94	Fawzy	1	1	0	0	0	0
95	Wachs	19	18	4	20	20	7
97	Beckett	2	2	0	1	1	1
98	Elist	1	1	1	0	0	0
100	Daboul	1	1	0	2	2	0
101	Freeman	3	3	1	4	4	2
102	Misurec	11	11	7	11	11	5
105	Kim	1	1	1	3	3	3
106	Freeman	3	3	2	3	3	2
109	Chu	3	3	0	4	4	2
110	Patsias	2	2	0	0	0	0
111	Rigby	1	1	1	0	0	0
115	Saslawsky	0	0	0	1	1	1
116	Wall	1	1	0	0	0	0
118	Gin-Shaw	8	7	2	8	8	1
119	Whitlock	2	2	0	3	3	1
120	Parramore	3	3	2	3	3	1
123	Castellano	3	3	0	3	3	2
124	Maggiacomo	3	3	0	2	2	0
125	Peters-Gee	4	4	3	2	2	0
127	Stallings	2	2	1	2	2	2
129	Ackerman	1	1	0	2	2	1
130	Nafziger	1	1	0	0	0	0
132	Kotkin	0	0	0	1	1	1
133	Vacker	2	2	0	2	2	1
137	George	2	2	0	2	2	1
138	Bowman	3	3	2	2	2	0
139	Nevins	2	2	2	2	2	1
141	Duffin	1	1	1	0	0	0
142	Efros	8	8	5	6	6	3

Site Number	Principal Investigator	Treatment Arm					
		Ciprofloxacin XR (N=521)			Ciprofloxacin BID (N=521)		
		Randomized	Valid for Safety	Per Protocol	Randomized	Valid for Safety	Per Protocol
145	Marks	0	0	0	1	1	0
148	Oberoi	14	14	3	14	14	5
149	Gezon	2	2	0	4	4	2
150	Swierzewski	2	2	1	1	1	0
151	Brownstone	5	5	3	5	5	1
153	Howard	0	0	0	1	1	0
155	Frankel	1	1	0	0	0	0
157	Phillips	1	1	0	1	1	1
159	Leff	0	0	0	1	1	0
160	Schneiderman	1	1	0	2	2	0
201	Casey	3	3	2	2	2	1
202	Valiquette	0	0	0	2	2	0
205	Shu	8	8	5	5	5	1
207	Nicolle	4	4	2	4	4	1
208	Nickel	2	2	1	0	0	0
209	O'Mahony	20	20	12	22	22	10
211	Barkin	5	5	1	4	4	0
213	Kuzmarov	3	3	1	3	3	0
TOTAL		**521**	**517**	**206**	**521**	**518**	**229**

TABLE 14
Bacteriological Eradication Rates at Test-of-Cure Visit (+5 to +11 days)
Patients Valid for Efficacy

Organism	Cipro XR			Cipro BID		
	Erad (%)	Pers (%)	Indeter (%)	Erad (%)	Pers (%)	Indeter (%)
Urine						
AUP Patients						
Escherichia coli	35 (97%)	1 (3%)	0	41 (100%)	0	0
cUTI Patients						
Escherichia coli	91 (97%)	3 (3%)	0	90 (98%)	2 (2%)	0
Klebsiella pneumoniae	20 (87%)	1 (4%)	2 (9%)	19 (83%)	4 (17%)	0
Enterococcus faecalis	17 (94%)	0	1 (6%)	14 (67%)	7 (33%)	0
Proteus mirabilis	11 (92%)	1 (8%)	0	10 (91%)	0	1 (9%)
Enterobacter aerogenes	4 (100%)	0	0	6 (100%)	0	0
Pseudomonas aeruginosa	3 (100%)	0	0	3 (100%)	0	0
Blood						
AUP Patients						
Escherichia coli	4 (80%)	0	1 (20%)	3 (75%)	0	1 (25%)
Klebsiella pneumoniae	1 (100%)	0	0	0	0	0
cUTI Patients						
Escherichia coli	1 (100%)	0	0	1 (100%)	0	0

Erad = eradication; Pers = persistence; Indeter = Indeterminate

Reviewer's Comment: Tables 15 through 19 are from the microbiologist's review.

TABLE 15
Microbiological Response by MIC for AUP Patients
Patients Valid for Efficacy

Organism	MIC (μg/mL)	Outcome	Cipro XR		Cipro BID	
			Number	%	Number	%
AUP Patients—Urine						
Escherichia coli	0.008	Eradication	1	100	3	100
	0.015	Eradication	24	96	25	100
		Persistence	1	4	0	0
	0.03	Eradication	6	100	7	100
	0.06	Eradication	2	100	2	100
	0.12	Eradication	1	100	1	100
	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	2	100
	ALL	Eradication	35	97	41	100
		Persistence	1	3	0	0
AUP Patients--Blood						
Escherichia coli	0.015	Eradication	4	80	0	0
		Indeterminate	1	20	1	100
	0.03	Eradication	0	0	1	100
	0.12	Eradication	0	0	1	100
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	80	3	75
		Indeterminate	1	20	1	25
Klebsiella pneumoniae	0.03	Eradication	1	100	0	0
	ALL	Eradication	1	100	0	0

TABLE 16
Microbiological Responses by MIC for cUTI Patients
Patients Valid for Efficacy

Organism	MIC (µg/mL)	Outcome	Cipro XR		Cipro BID	
			Number	%	Number	%
cUTI Patients--Urine						
Escherichia coli	0.008	Eradication	10	100	6	100
	0.015	Eradication	54	98	50	98
		Persistence	1	2	1	2
	0.03	Eradication	19	100	24	100
	0.06	Eradication	4	80	3	100
		Persistence	1	20	0	0
	0.12	Eradication	0	0	5	100
	0.25	Eradication	2	100	1	50
		Persistence	0	0	1	50
	0.5	Eradication	2	67	0	0
		Persistence	1	33	0	0
	1.0	Eradication	0	0	1	100
	ALL	Eradication	91	97	90	98
		Persistence	3	3	2	2
Enterococcus faecalis	0.25	Eradication	0	0	1	50
		Persistence	0	0	1	50
	0.5	Eradication	6	100	3	50
		Persistence	0	0	3	50
	1	Eradication	11	100	8	89
		Persistence	0	0	1	11
	2	Eradication	0	0	2	50
		Persistence	0	0	2	50
		Indeterminate	1	100	0	0
	ALL	Eradication	17	94	14	67
		Persistence	0	0	7	33
		Indeterminate	1	6	0	0
Klebsiella pneumoniae	0.015	Eradication	1	100	1	100
	0.03	Eradication	4	67	10	83
		Persistence	0	0	2	17
		Indeterminate	2	33	0	0
	0.06	Eradication	5	83	4	67
		Persistence	1	17	2	33
	0.12	Eradication	2	100	1	100
	0.25	Eradication	4	100	0	0
	0.5	Eradication	2	100	2	100
	1.0	Eradication	2	100	1	100
	ALL	Eradication	20	87	19	83
		Persistence	1	4	4	17
		Indeterminate	2	9	0	0
Proteus mirabilis	0.015	Eradication	2	100	0	0
	0.03	Eradication	5	100	5	100
	0.06	Eradication	3	75	1	100
		Persistence	1	25	0	0
	0.12	Eradication	0	0	1	100
	0.5	Indeterminate	0	0	1	100
	1	Eradication	1	100	0	0

Organism	MIC (μg/mL)	Outcome	Cipro XR		Cipro BID	
			Number	%	Number	%
	2	Eradication	0	0	3	100
	ALL	Eradication	11	92	10	91
		Persistence	1	8	0	0
		Indeterminate	0	0	1	9
Enterobacter aerogenes	0.015	Eradication	1	100	1	100
	0.03	Eradication	1	100	4	100
	0.06	Eradication	2	100	0	0
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	100	6	100
Pseudomonas	0.12	Eradication	2	100	2	100
aeruginosa	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	0	0
	ALL	Eradication	3	100	3	100
cUTI Patients—Blood						
Escherichia coli	0.015	Eradication	1	100	0	0
	012	Eradication	0	0	1	100
	ALL	Eradication	1	100	1	100

Reviewer's Comment: Tables 17 and 18 were modified from the microbiologist's review by the reviewer for clarity.

TABLE 17
Patients with Bacteriologic Persistence or Clinical Failure
Cipro XR Group
Patients Valid for Efficacy

Patient #	Organism	Cipro MIC	Bact Resp At TOC	Bact Resp At FU	Clin Resp At TOC	Clin Resp At FU
15005	*E. coli*	0.06	Persistence	Persistence	Cure	
31006	*P. mirabilis*	0.06	Persistence	Persistence	Cure	Relapse
31012	*E. faecalis*	1.0	Eradication	Indeterminate	Failure	Failure
42012	*S. aureus*	2.0	Persistence	Persistence	Cure	
42056	*C. freundii*	0.12	Persistence	Persistence	Failure	Failure
48037	*S. aureus*	0.25	Persistence	Persistence	Cure	
49061	*E. coli*	0.5	Persistence	Persistence	Cure	Con. Cure
73042	*K. pneumoniae*	0.25	Eradication	Indeterminate	Failure	Failure
77018	*E. coli*	0.015	Persistence	Persistence	Relapse	Relapse
98001	*K. pneumoniae*	0.06	Persistence	Persistence	Cure	Failure
125006	*K. pneumoniae*	0.25	Eradication	Indeterminate	Failure	Failure
127001	*E. faecalis*	2.0	Indeterminate	Indeterminate	Failure	Failure
127001	*K. pneumoniae*	0.03	Indeterminate	Indeterminate	Failure	Failure
209029	*E. coli*	0.015	Persistence	Persistence	Cure	Relapse
209039	*E. faecalis*	1.0	Persistence	Persistence	Failure	Failure

Cipro = ciprofloxacin; Bact Resp = bacteriological response; Clin Resp = clinical response
TOC = test-of-cure; FU = follow-up
Con. Cure = continued cure; Con. Erad. = continued eradication

TABLE 18
Patients with Bacteriologic Persistence or Clinical Failure
Cipro BID Group
Patients Valid for Efficacy

Patient #	Organism	Cipro MIC	Bact Resp At TOC	Bact Resp At FU	Clin Resp At TOC	Clin Resp At FU
12002	*E. coli*	0.015	Eradication	Indeterminate	Failure	Failure
13017	*E. faecalis*	1.0	Persistence	Persistence	Cure	Con. Cure
15011	*K. pneumoniae*	0.03	Persistence	Persistence	Cure	Relapse
25005	*K. oxytoca*	0.5	Persistence	Persistence	Cure	Relapse
25029	*E. faecalis*	1.0	Persistence	Persistence	Cure	Con. Cure
25029	*E. coli*	0.03	Eradication	Con. Erad	Cure	Con. Cure
42038	*C. koseri*	0.5	Persistence	Persistence	Cure	Failure
45019	*E. faecalis*	0.5	Persistence	Persistence		
48013	*E. coli*	0.03	Eradication	Indeterminate	Failure	Failure
53029	*K. pneumoniae*	0.06	Eradication	Persistence	Failure	Failure
59033	*K. pneumoniae*	0.5	Eradication	Indeterminate	Failure	Failure
73046	*E. faecalis*	0.25	Persistence	Persistence	Cure	Con. Cure
73046	*E. coli*	0.015	Eradication	Con. Erad	Cure	Con. Cure
74015	*K. pneumoniae*	0.03	Persistence	Persistence	Failure	Failure
76011	*K. pneumoniae*	0.06	Persistence	Persistence	Failure	Failure
77006	*E. coli*	0.015	Persistence	Persistence		
91008	*E. coli*	0.25	Persistence	Persistence	Failure	Failure
92011	*E. faecalis*	1.0	Eradication	Indeterminate	Failure	Failure
92011	*S. marcescens*	1.0	Eradication	Indeterminate	Failure	Failure
97001	*S. aureus*	0.5	Persistence	Persistence	Relapse	Relapse
101007	*E. faecalis*	2.0	Persistence	Persistence	Cure	
106019	*K. pneumoniae*	0.03	Eradication	Indeterminate	Failure	Failure
127006	*E. faecalis*	0.5	Persistence	Persistence	Failure	Failure
129001	*E. faecalis*	2.0	Persistence	Persistence	Failure	Failure
133008	*E. coli*	0.03	Eradication	Indeterminate	Failure	Failure
201006	*E. faecalis*	0.5	Persistence	Persistence	Failure	Failure

Cipro = ciprofloxacin; Bact Resp = bacteriological response; Clin Resp = clinical response
TOC = test-of-cure; FU = follow-up
Con. Cure = continued cure; Con. Erad. = continued eradication

TABLE 19
Organisms with Elevated MICs Post-Therapy[a]

Organism	MIC (µg/mL)		Eradication	
	Pre-Therapy	Post-Therapy	TOC	FU
Escherichia coli				
Cipro XR group	0.015	0.12	No	No
	0.03	0.5	Yes	Recurred
	0.03	16	Yes	Recurred
	0.06	16	Yes	Recurred
Cipro BID group	0.015	0.5	Yes	Recurred
	0.015	1.0	Yes	Recurred
	0.015	16	No	No
Enterococcus faecalis				
Cipro BID group	0.5	2	No	No
	1	16	No	No
Klebsiella pneumoniae				
Cipro XR group	0.06	0.5	No	No
Staphylococcus aureus				
Cipro XR group	2	16	No	No

[a] MIC at post-therapy greater than one dilution higher than MIC at pre-therapy

TABLE 40
Number of Patients (%) with Bacteriological Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Safety

	Cipro XR	**Cipro BID**
All Patients	(N=327)	(N=315)
Eradication	207 (63.3%)	214 (67.9%)
Persistence	24 (7.3%)	33 (10.5)
Superinfection	5 (1.5%)	3 (1.0%)
New infection	9 (2.8%)	16 (5.1%)
Indeterminate	82 (25.1%)	49 (15.6%)
Eradication Rate[a]	**207/327 (63.3%)**	**214/327 (67.9%)**
AUP Patients	(N=71)	(N=76)
Eradication	47 (66.2%)	58 (76.3%)
Persistence	3 (4.2%)	3 (3.9%)
New infection	3 (4.2%)	1 (1.3%)
Indeterminate	18 (25.4%)	14 (18.4%)
cUTI Patients	(N=256)	(N=239)
Eradication	160 (62.5%)	156 (65.3%)
Persistence	21 (8.2%)	30 (12.6%)
Superinfection	5 (2.0%)	3 (1.0%)
New infection	6 (2.3%)	15 (6.3%)
Indeterminate	64 (25.0%)	35 (14.6%)

[a] Eradication rate for all patients (cUTI plus AUP), including indeterminate responses; Estimate of the difference in rates –4.4% [Mantel-Haenszel 95% CI (-11.8%, 2.9%)]

TABLE 41
Number of Patients (%) with Bacteriological Response at the Follow-up Visit (+28 to +42 Days)
Patients Valid for Safety

	Cipro XR	**Cipro BID**
All Patients	(N=327)	(N=315)
Continued eradication	146 (44.6%)	130 (41.3%)
Eradication w/recurrence	22 (6.7%)	24 (7.6%)
Persistence	24 (7.3%)	31 (9.8%)
Superinfection	5 (1.5%)	2 (0.6%)
New infection	30 (9.2%)	42 (13.3%)
Indeterminate	100 (30.6%)	86 (27.3%)
Eradication Rate[a]	**146/327 (44.6%)**	**130/315 (41.3%)**
AUP Patients	(N=71)	(N=76)
Continued eradication	35 (49.3)	41 (53.9%)
Eradication w/recurrence	1 (1.4%)	4 (%.3%)
Persistence	3 (4.2%)	3 (3.9%)
New infection	5 (7.0%)	5 (6.6%)
Indeterminate	27 (38.0%)	23 (30.3%)
Continued Eradication Rate[b]	**35/71 (49.3)**	**41/76 (53.9%)**
cUTI Patients	(N=256)	(N=239)
Continued eradication	111 (43.4%)	89 (37.2%)
Eradication w/recurrence	21 (8.2%)	20 (8.4%)
Persistence	21 (8.2%)	28 (11.7%)
Superinfection	5 (2.0%)	2 (0.8%)
New infection	25 (9.8%)	37 (15.5%)
Indeterminate	73 (28.5%)	63 (26.4%)
Continued Eradication Rate[c]	**111/256 (43.4%)**	**89/239 (37.2%)**

[a] Eradication rate for all patients (cUTI plus AUP); the follow-up rates in this population include the indeterminate responses. Estimate of the difference in rates 3.6% [Mantel-Haenszel 95% CI (-4.0%, 11.3%)]
[b] Continued eradication rate for AUP patients, including indeterminate responses.
[c] Continued eradication rate for cUTI patients, including indeterminate responses.

TABLE 42
Number of Patients (%) with Clinical Response at the TOC Visit (+5 to +11 Days)
Patients Valid for Safety

	Cipro XR	**Cipro BID**
All Patients	(N=517)	(N=518)
Cure	343 (66.3%)	366 (70.7%)
Continued cure	0 (0%)	1 (0.2%)
Improvement	0 (0%)	1 (0.2%)
Failure	35 (6.8%)	38 (7.3%)
Relapse	1 (0.2%)	1 (0.2%)
Indeterminate	11 (2.1%)	8 (1.5%)
Missing	127 (24.6%)	103 (19.9%)
Success Rate[a]	**343/517 (66.3%)**	**367/518 (70.8%)**
AUP Patients	(N=109)	(N=111)
Cure	76 (69.7%)	85 (76.6%)
Continued cure	0 (0%)	1 (0.9%)
Improvement	0 (0%)	1 (0.9%)
Failure	6 (5.5%)	4 (3.6%)
Indeterminate	2 (1.8%)	1 (0.9%)
Missing	25 (22.9%)	19 (17.1%)
cUTI Patients	(N=408)	(N=407)
Cure	267 (65.4%)	281 (69.0%)
Failure	29 (7.1%)	34 (98.4%)
Relapse	1 (0.2%)	1 (0.2%)
Indeterminate	9 (2.2%)	7 (1.7%)
Missing	102 (25.0%)	84 (20.6%)

[a] Success rate (cure plus continued cure) for all patients (cUTI plus AUP), including indeterminate or missing responses; Estimate of the difference in rates – 4.5%;[Mantel-Haenszel 95% CI (-10.1%, 1.2%)]

TABLE 43
Number of Patients (%) with Clinical Response at the Follow-up Visit (+28 to +42 Days)
Patients Valid for Safety

	Cipro XR	**Cipro BID**
All Patients	(N=517)	(N=518)
Cure	1 (0.2%)	1 (0.2%)
Continued cure	257 (49.7%)	269 (51.9%)
Failure	41 (7.9%)	43 (8.3%)
Relapse	33 (6.4%)	34 (6.6%)
Indeterminate	3 (0.6%)	7 (1.4%)
Missing	182 (35.2%)	164 (31.7%)
Success Rate[a]	**258/517 (49.9%)**	**270/518 (52.1%)**
AUP Patients	(N=109)	(N=111)
Cure	1 (0.9%)	0 (0%)
Continued cure	59 (54.1%)	68 (61.3%)
Failure	6 (5.5%)	4 (3.6%)
Relapse	8 (7.3%)	0 (0%)
Missing	35 (32.1%)	39 (35.1%)
Success Rate[b]	**60/109 (55.0%)**	**68/111 (61.3%)**
cUTI Patients	(N=408)	(N=407)
Cure	0 (0%)	1 (0.2%)
Continued cure	198 (48.5%)	201 (49.4%)
Failure	35 (8.6%)	39 (99.6%)
Relapse	25 (6.1%)	34 (8.4%)
Indeterminate	3 (0.7%)	7 (1.7%)
Missing	147 (36.0%)	125 (30.7%)
Success Rate[c]	**198/408 (48.5%)**	**201/407 (49.4%)**

[a] Success rate (cure plus continued cure) for all patients (cUTI plus AUP), including missing or indeterminate responses; Estimate of difference in rates –2.2% [Mantel-Haenszel 95% CI (-8.27%, 3.9%)]
[b] Success rate (cure plus continued cure) for pyelonephritis patients, including missing or indeterminate responses.
[c] Success rate (cure plus continued cure) for complicated UTI patients, including missing or indeterminate responses.

Tables 47A, 47B, 48A and 48B were created by the reviewer.

TABLE 47A
Summary of Adverse Events
Patients Valid for Safety with Normal Renal Function CLcr > 80 mL/min

	Cipro XR (N=321)	Ciprofloxacin BID (N=323)
Any adverse event	88 (27.4%)	65 (20.1%)
Any drug-related adverse event*	34 (10.6%)	29 (9.0%)
Any serious adverse event	25 (7.8%)	15 (4.6%)

* possible, probable, and likely

TABLE 47B
Summary of Adverse Events
Patients Valid for Safety with Moderate Renal Impairment
CLcr = 30 to 50 mL/min

	Cipro XR (N=106)	Ciprofloxacin BID (N=96)
Any adverse event	33 (31.1%)	29 (30.2%)
Any drug-related adverse event*	13 (12.3%)	11 (11.5%)
Any serious adverse event	4 (3.8%)	5 (5.2%)

* possible, probable, and likely

TABLE 48A
Incidence Rates of Adverse Events Occurring in at Least 2 Patients by Treatment Group
Patients Valid for Safety with a Creatinine Clearance between 30 to 50 mL/min

Cipro XR (N=106)	n	%		Cipro BID (N=97)	n	%
NAUSEA	7	6.6		NAUSEA	8	8.2
DIARRHEA	5	4.7		DYSPEPSIA	4	4.1
DIZZINESS	4	3.8		PRURITUS	3	3.1
ASTHENIA	2	1.9		VOMITING	3	3.1
COLITIS	2	1.9		ACCIDENTAL INJURY	2	2.1
DEHYDRATION	2	1.9		ANOREXIA	2	2.1
FEVER	2	1.9		CORONARY ARTERY DISORDER	2	2.1
HEADACHE	2	1.9		DIARRHEA	2	2.1
HEMATURIA	2	1.9		DIZZINESS	2	2.1
HYPERTENSION	2	1.9		HEADACHE	2	2.1
MALAISE	2	1.9		HEMORRHAGE	2	2.1
PERIPHERAL EDEMA	2	1.9		LIVER FUNCTION TESTS ABNORMAL	2	2.1
PNEUMONIA	2	1.9		PERIPHERAL EDEMA	2	2.1
SEPSIS	2	1.9				
UROGENITAL SURGERY	2	1.9				
VAGINAL MONILIASIS	2	1.9				
VOMITING	2	1.9				

TABLE 48B
Incidence Rates of Adverse Events Occurring in at Least 2 Patients by Treatment Group
Patients Valid for Safety with a Creatinine Clearance above 80 mL/min

Cipro XR (N=322)	n	%		Cipro BID (N=324)	n	%
HEADACHE	14	4.3		HEADACHE	19	5.9
NAUSEA	12	3.7		NAUSEA	11	3.4
DIARRHEA	9	2.8		DIARRHEA	7	2.2
VOMITING	9	2.8		DIZZINESS	7	2.2
VAGINAL MONILIASIS	7	2.2		LIVER FUNCTION TESTS ABNORMAL	7	2.2
DIZZINESS	6	1.9		VAGINAL MONILIASIS	7	2.2
DYSPEPSIA	6	1.9		CONSTIPATION	5	1.5
ABDOMINAL PAIN	3	0.9		ABDOMINAL PAIN	4	1.2
ARTHRALGIA	3	0.9		ACCIDENTAL INJURY	4	1.2
BACK PAIN	3	0.9		ARTHRALGIA	4	1.2
FLATULENCE	3	0.9		BACK PAIN	4	1.2
PHARYNGITIS	3	0.9		SINUSITIS	4	1.2
RHINITIS	3	0.9		FEVER	3	0.9
URINARY RETENTION	3	0.9		INSOMNIA	3	0.9
VAGINITIS	3	0.9		VAGINITIS	3	0.9
ANOREXIA	2	0.6		VOMITING	3	0.9
ASTHENIA	2	0.6		ANOREXIA	2	0.6
CONSTIPATION	2	0.6		ANXIETY	2	0.6
CYST	2	0.6		ARTHRITIS	2	0.6
DEHYDRATION	2	0.6		ASTHENIA	2	0.6
DYSURIA	2	0.6		COUGH INCREASED	2	0.6
FLU SYNDROME	2	0.6		DYSURIA	2	0.6
HYPERTONIA	2	0.6		FLATULENCE	2	0.6
INFECTION BACTERIAL	2	0.6		GI NEOPLASIA	2	0.6
INSOMNIA	2	0.6		LEG PAIN	2	0.6
KIDNEY CALCULUS	2	0.6		LUNG DISORDER	2	0.6
LIVER FUNCTION TESTS ABNORMAL	2	0.6		MYASTHENIA	2	0.6
MYALGIA	2	0.6		ORAL MONILIASIS	2	0.6
PELVIC PAIN	2	0.6		RECTAL HEMORRHAGE	2	0.6
PERIPHERAL EDEMA	2	0.6		RHINITIS	2	0.6
RASH	2	0.6		SEPSIS	2	0.6
SPECIAL SENSES SURGERY	2	0.6				

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/s/

Joette Meyer
9/3/03 11:53:31 AM
MEDICAL OFFICER

Rigoberto Roca
9/3/03 12:38:02 PM
MEDICAL OFFICER

Renata Albrecht
9/5/03 03:15:54 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

CHEMISTRY REVIEW(S)

NDA 21-554

CIPRO XR (ciprofloxacin extended-release tablets), 1000-mg

BAYER PHARMACEUTICALS CORPORATION

Dorota Matecka
Division of Special Pathogen and Immunologic Drug Products, HFD-590

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-554

2. REVIEW #: 1

3. REVIEW DATE: 27-Aug-2003

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-Oct-2002
Amendment (BC)	20-Jan-2003
Amendment (BC)	6-Jun-2003
Amendment (BC)	5-Aug-2003

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Original	29-Oct-2002
Amendment (BC)	20-Jan-2003
Amendment (BC)	6-Jun-2003
Amendment (BC)	5-Aug-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Bayer Pharmaceuticals Corporation
Address:	400 Morgan Lane, West Haven, CT 06516
Representative:	Andrew Verderame, Associate Director, Regulatory Affairs
Telephone:	(203) 812-5172

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CIPRO XR
b) Non-Proprietary Name (USAN): ciprofloxacin extended-release tablets
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: antibacterial

11. DOSAGE FORM: extended-release tablets

12. STRENGTH/POTENCY: 1000 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

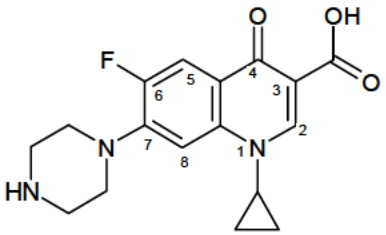
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

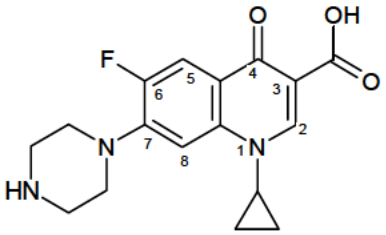
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ciprofloxacin hydrochloride (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride (mixture of monohydrate and sesquihydrate); $C_{17}H_{18}N_3FO_3$ x HCl (H_2O and 1.5 H_2O); 367.8 (anhydrate); 385.8 (monohydrate)



• HCl
• H_2O

Ciprofloxacin [redacted] (b) (4) (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid); $C_{17}H_{18}N_3FO_3$ (anhydrous basis); $C_{17}H_{18}N_3FO_3$ x 3.5 H_2O (3.5 hydrate); 331.4 (anhydrate); 394.3 (3.5 hydrate)



• $3.5H_2O$

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
8134	II	Bayer AG	Ciprofloxacin HCl	1	Adequate	20-Aug-2003	N/A
10353	II	Bayer AG	Ciprofloxacin (b) (4)	1	Adequate	9-Dec-2002	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
	III	(b) (4)	(b) (4)	3* and 4	Adequate	12/13/99	N/A
	III	(b) (4)	(b) (4)	3* and 4	Adequate	6/30/99	Acceptable for LR-734-45
	III	(b) (4)	(b) (4)	3* and 4	Adequate	12/19/00	N/A
	III	(b) (4)	(b) (4)	3* and 4	Adequate	7/13/99 and 7/26/00	N/A
	III	(b) (4)	(b) (4)	3	Adequate	4/25/02	N/A
	III	(b) (4)	(b) (4)	3* and 4		12/03/97	N/A
	III	(b) (4)	(b) (4)	3	Adequate	9/18/00	Acceptable for 75M seal
	III	(b) (4)	(b) (4)	3	Adequate	6/06/02	Acceptable for PH010B2
	III	(b) (4)	(b) (4)	3	Adequate	1. 8/23/02 2. 6/13/02	N/A

* Reviewed previously, as indicated by the review date received from the Comis database. It was not verified if any revisions were made since the last review, however for this NDA, sufficient information regarding the container/closure systems for the drug product was provided in the application as described in the review below

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,331	Ciprofloxacin extended-release tablets
NDA	21-473	CIPRO XR Tablets, 500-mg

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	17-Dec-2002	Janine D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Not submitted yet	N/A	N/A
DMETS	N/A	N/A	N/A
EA	Categorical exclusion	N/A	N/A
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-554

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, ciprofloxacin, is a synthetic broad-spectrum antimicrobial agent available on the market in several other formulations (e.g. CIPRO Tablets, CIPRO I.V., and CIPRO XR tablets, 500-mg).

CIPRO XR tablets contain two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and Ciprofloxacin (b) (4) (hydrated form of ciprofloxacin base).

For the majority of chemistry, manufacturing and controls information regarding ciprofloxacin hydrochloride the reference is made to DMF Type II 8134 held by Bayer AG. The retest period for the ciprofloxacin hydrochloride drug substance is (b) (4).

For the majority of chemistry, manufacturing and controls information regarding Ciprofloxacin (b) (4) reference is made to DMF Type II 10353 held by Bayer AG. Ciprofloxacin (b) (4) is a hydrated form of ciprofloxacin base, which consists mainly of the 3.5 hydrate (theoretically (b) (4) of water per molecule of ciprofloxacin). The information regarding the (b) (4) of Ciprofloxacin (b) (4) is provided in both DMF and NDA. Ciprofloxacin (b) (4) for the use in CIPRO XR tablets (b) (4). The (b) (4) step description and the specification for the (b) (4) Ciprofloxacin (b) (4) are provided in the NDA. The retest period for the Ciprofloxacin (b) (4) drug substance is 12 months.

CIPRO XR tablets have been developed, based on conventional (b) (4) principle (with (b) (4) as the retardation agent), as (b) (4) two-layer tablets with the following characteristics:

- 2-layer tablet with IR (immediate release) layer for fast dissolution of the drug and absorption in the upper GI tract, and CR (controlled release) layer for achievement of sufficient plasma levels over a prolonged period of time;

- 2 types of ciprofloxacin (ciprofloxacin hydrochloride and ciprofloxacin base, both in each layer in different proportion), which contribute to minimize pH dependent effects on dissolution

Each CIPRO XR 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin hydrochloride (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (425.2 mg, calculated on the dried basis).

CIPRO XR 500 mg tablets (containing identical active and inactive components) for a once-a-day treatment of uncomplicated urinary tract infections have been approved previously (December 2002) via NDA 21-473.

B. Description of How the Drug Product is Intended to be Used

CIPRO XR tablets are available as 1000-mg coated tablets for a once-a-day treatment of complicated urinary tract infections. The tablets are packaged in three packaging configurations, HDPE 250 cc bottles (of 100 tablets), HDPE 150 cc bottles (of 50 tablets), and PVC/PVDC clear blisters with laminated foil backing.

The proposed expiration dating of 24 months as proposed by the applicant for CIPRO XR tablets, 1000 mg is acceptable. The storage conditions statement recommends the storage at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of CIPRO XR (ciprofloxacin extended-release tablets), 1000-mg. During the review a number of issues, including the following, were resolved.

The specification for one of the drug substances (ciprofloxacin base), specifically the acceptance criteria for the loss on drying and the particle size distribution were revised.

The specification for the drug product was also revised to include test and acceptance criteria for water content. Acceptance criteria for the impurities in the drug product were revised.

The trade name was found acceptable by OPDRA (now ODS) and by the Division HFD-590 for NDA 21-473. The established name was further consulted with the Labeling and Nomenclature Committee and it was recommended as following:

CIPRO XR (ciprofloxacin* extended-release tablets)

* as ciprofloxacin † and ciprofloxacin hydrochloride
† does not comply with the loss on drying test and residue on ignition test of the USP monograph.

III. Administrative

A. Reviewer's Signature

DFS (electronic)

B. Endorsement Block

Chemist: Dorota Matecka/08/15/03
Chemistry TL: Norman Schmuff
PM: Jouhayna Saliba

C. CC Block

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/s/

Dorota Matecka
8/28/03 09:55:45 AM
CHEMIST

Norman Schmuff
8/30/03 01:56:44 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA: 21-554
Review Number: 1
Date of Submission: 10/29/02
Information to Sponsor: Yes ( ) No (X)

Sponsor: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

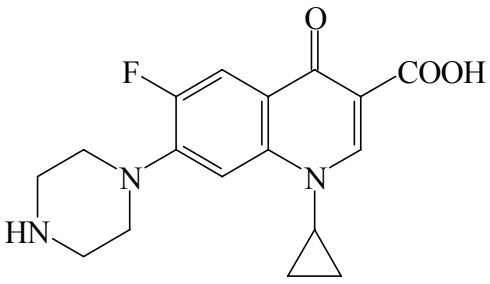
Manufacturer of Drug Substance:
Bayer AG
D-51368 Leverkusen
Germany

Reviewer: Stephen G. Hundley, Ph.D, DABT
Pharmacology/Toxicology Reviewer

Division: Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 3/3/03

Drug Product: Cipro XR (1000 mg tablet)
Generic Name: Cipro®
Code Name: Not Applicable
Drug Substance: Ciprofloxacin HCl and Ciprofloxacin betaine (base)
Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[1-piperazinyl] -3-quinoline-carboxylic acid
CAS#: 85721-33-1
Molecular Formula: $C_{17}H_{18}FN_3O_3$
Molecular Weight: 331.4 (385.8 for the monochloride monohydrate salt)
Molecular Structure:



Relevant IND: 61,331

Drug Class: Antimicrobial Fluoroquinolone

Indication: Complicated Urinary Tract Infection and Acute Uncomplicated Pyelonephritis

Clinical Formulation: Extended Release Tablet

Route of Administration: Oral

Proposed Use: Single 1000 mg Cipro XR tablet daily for 7 to 14 consecutive days.

Executive Summary

Recommendations:

Approvability – The NDA submission is approvable from the perspective of nonclinical pharmacology and toxicology.

Nonclinical Studies – Additional nonclinical studies are not required.

Labeling – The sponsor's proposed label is acceptable with regard to the nonclinical pharmacology and toxicology portions of the label.

Summary of Nonclinical Findings:

Previously submitted nonclinical studies supported the approval of ciprofloxacin (CIPRO®) for several indications under NDA's 19-537, 20-780, 19-857, 19-858, and 19-847. Included in the approved indications are acute sinusitis, acute exacerbation of chronic bronchitis, bacterial prostatitis, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections, and lower respiratory tract infections. Critical evaluation of previously submitted nonclinical toxicology studies with ciprofloxacin supported the conduct of clinical trials for complicated bone and joint infections where the dosing regimen was 750 mg ciprofloxacin b.i.d., for a period up to six weeks. The same nonclinical data base is more than sufficient to support the current indication for treatment of complicated urinary tract infection and acute uncomplicated pyelonephritis with Cipro XR at a 1000 mg daily dose of ciprofloxacin for a period of 7 to 14 days.

No additional Pharmacology/Toxicology NDA Review is provided beyond the Cover Sheet and Executive Summary.

_____

Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Concurrence:

_____

Kenneth Hastings, Dr. P.H., DABT
Pharmacology/Toxicology Supervisor & Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

cc:

HFD-590/CSO/S. Peacock
HFD-590/MO/M. Ruiz
HFD-590/MO/R. Roca
HFD-590/Biopharm/D. Chilukuri
HFD-590/Micro/P. Dionne
HFD-590/Chem/D. Matecka

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/s/

Steve Hundley
3/5/03 11:45:53 AM
PHARMACOLOGIST

Kenneth Hastings
3/5/03 12:48:42 PM
PHARMACOLOGIST

Renata Albrecht
3/29/03 09:08:16 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-554
Names of drug:	Cipro XR
Applicant:	Bayer
Indication:	Complicated Urinary Tract Infection
Documents reviewed:	\\CDSESUB1\N21554\N_000\2002-10-29\
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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

It is the opinion of this reviewer that Cipro XR has been shown to be non-inferior to Cipro® in terms of the bacteriologic endpoint at TOC in cUTI subjects. Noninferiority of Cipro XR in comparison to Cipro® in terms of the bacteriologic endpoint at TOC within AUP subjects has not been demonstrated.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR in the treatment of complicated urinary tract infection. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily (QD) (b) (4) Tablets 1000 mg versus Conventional Ciprofloxacin 500 mg Tablets BID in the 7 to 14 Day Treatment of Patients with Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis". This study will be thoroughly reviewed within this document.

1.3 PRINCIPAL FINDINGS

For the controlled clinical trial submitted in support of the efficacy of Cipro XR, the by-treatment group comparisons of the primary efficacy endpoint (i.e., bacteriologic outcome at TOC) were not consistent across infection types. A treatment-by-infection-type interaction was observed indicating that the treatment effect is different for AUP patients and cUTI patients and as such these two strata should be considered separately.

Within the cUTI stratum, it is the opinion of this reviewer that Cipro XR has been shown to be noninferior to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group. Disproportionately more subjects in the Cipro XR arm were excluded from the PP analysis group for no valid TOC urine culture (which most commonly was due to adverse event or protocol violation). The majority of these subjects were considered failures in the mITT analysis since their bacteriological response at TOC was likely missing or indeterminate. Within the cUTI stratum in the mITT group, the noninferiority criterion was not met.

Within the AUP stratum, it is the opinion of this reviewer that noninferiority of Cipro XR to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group has not been demonstrated. In fact within the AUP stratum, Cipro XR is nearly statistically significantly worse than Cipro® for the eradication at TOC endpoint in the PP analysis group. A similar trend is observed in the mITT group for this endpoint.

Secondary endpoints for this study included the bacteriological response at follow-up and clinical responses at TOC and follow-up.

- The eradication rates at follow-up for the cUTI subjects were higher in the Cipro XR group than in the Cipro® group. Conversly, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro® group than in the Cipro XR group. These trends are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata.
- The clinical success rates at TOC for the cUTI subjects in the PP analysis group were slightly higher in the Cipro XR group than in the Cipro® group. The clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro® and Cipro XR groups in the PP analysis group. The Cipro XR group had slightly lower clinical success rates than the Cipro® group in the mITT analysis.
- The clinical success rates at the follow-up visit for the cUTI subjects in the PP analysis group were higher in the Cipro XR group than in the Cipro® group. Conversely, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR group than in the Cipro® group in the PP analysis group. Similar trends were observed in the mITT analysis. These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint.

Examination of the primary efficacy endpoint by age, race, and gender indicated that in cUTI subjects, the difference in eradication rates between the two treatment groups was greatest in the age group 65 to 74 years. Also for cUTI subjects, the differences in eradication rates were fairly constant across races. And the difference in eradication rates was larger for males than females in cUTI subjects. The differences in eradication rates in AUP subjects between the two treatment groups were difficult to judge because of the small number of subjects in each subcategory but appeared to be fairly constant across age, race, and gender subcategories.

Tabulations of the bacteriologic success at the TOC visit were fairly numerically consistent across treatment groups for each of the organisms studied.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR for the treatment of complicated urinary tract infection and acute uncomplicated pyelonephritis. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily (QD) (b) (4) Tablets 1000 mg versus Conventional Ciprofloxacin 500 mg Tablets BID in the 7 to 14 Day Treatment of Patients with Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis". The primary objective of the study was to prove that the bacteriological eradication rate using Cipro XR is not inferior to that of conventional Ciprofloxacin at the test of cure visit in patients with complicated urinary tract infections or acute uncomplicated pyelonephritis.

2.2 DATA ANALYZED AND SOURCES

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR for the treatment of complicated urinary tract infection and acute uncomplicated pyelonephritis. The following data sets were submitted electronically and utilized in the review of this study.

\\CDSESUB1\N21554\N_000\2002-10-29\crt\datasets\100275\analysis.xpt
\\CDSESUB1\N21554\N_000\2002-10-29\crt\datasets\100275\visit.xpt

At the reviewer's request (at the pre-NDA meeting) the sponsor created and submitted the analysis.xpt data set. The analysis.xpt data set was particularly helpful in the investigation of the efficacy results and this reviewer is appreciative of the sponsor's willingness to submit the data in this format. All submitted data sets were found to be clearly documented and well organized.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 REVIEW OF STUDY NUMBER BAY-Q3939-100275

2.3.1.1 Study Design, Protocol, and Protocol Amendments

This was a multicenter, prospective, randomized, double-blind, parallel group, phase III clinical trial conducted at 100 centers in the United States and Canada. The primary objective of this study was to determine if Cipro XR 1000 mg PO QD for seven to fourteen days was non-inferior to conventional ciprofloxacin (Cipro®) 500 mg PO BID for seven to fourteen days in the treatment of patients with complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP).

Patients who fulfilled the following protocol-specified criteria were eligible for inclusion in the study.

- Men or non-pregnant women, 18 years of age or older;
- For cUTI, patients must have presented with one or more of the following: dysuria, urgency, frequency, suprapubic pain, back pain, flank pain, CVA pain and tenderness, and fever (>38^{O} C/100.4^{O} F orally) with or without chills;
- For cUTI patients must have at least one or more the following underlying conditions: indewelling urinary catheter, 100 mL of residual urine after voiding, neurogenic bladder, obstructive uropathy due to nephrolithiasis, tumor or fibrosis, and urinary retention in men possibly due to benign prostatic hypertrophy;
- For AUP, patients must have presented with clinical signs and symptoms of an ascending UTI, manifested by all three of the following: fever (>38^{O} C/100.4^{O} F orally), chills, and flank pain;
- For AUP, patients may also have had any of the following: CVA tenderness, nausea, dysuria, nocturia, frequency, urgency, suprapubic or lower back pain;
- Onset of symptoms ≤72 hours prior to study entry (original protocol dated 01/11/2001) Timing of onset of symptoms not restricted (amendment 4 dated 09/17/2001);

- Women of childbearing potential were required to use two reliable methods of contraception during exposure to study drug; and
- Obtained one pretreatment clean-catch midstream urine sample within 48 hours of enrollment in the study (study enrollment and treatment were permitted prior to the availability of urine culture results).

For purposes of the efficacy analysis subjects must have, a positive culture (defined as $\geq 10^5$ CFU/mL for a causative pathogen), pyuria (defined as ≥ 10 leukocytes/mm^3 in unspun urine specimens or >5 WBC/hpf in spun urine specimens), and a causative pathogen(s) that is susceptible to ciprofloxacin in vitro. For complete listing of exclusion criteria, please see study protocol.

After the inclusion/exclusion criteria were satisfied and written informed consent was obtained, patients were stratified based on the presence or absence of AUP (stratum 1: patients with AUP, stratum 2: patients without AUP but with cUTI) and randomly assigned to receive one of the following two treatments.

Cipro XR 1000 mg QD for seven to fourteen days or
Cipro® 500 mg BID for seven to fourteen days

The primary efficacy variable was defined to be the bacteriological response at the test-of-cure visit (TOC). Bacteriological response at the TOC visit was graded as eradication, persistence, superinfection, new infection, or indeterminate. The following definitions are from the sponsor's study report.

Eradication: A urine culture, obtained within the Days +5 to +11 posttreatment window, showing that all uropathogens found at study entry in a quantity $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL.
Persistence: A urine culture obtained any time after the completion of therapy, grew $\geq 10^4$ CFU/mL of the original uropathogen.
Superinfection: A urine culture grew $\geq 10^5$ CFU/ml of a uropathogen other than the baseline pathogen at any time during the course of active therapy.
New Infection: A pathogen, other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/mL, was present at a level $\geq 10^5$ CFU/mL anytime after treatment was completed.
Indeterminate: It was not possible to determine bacteriological outcome. The reason for an indeterminate evaluation must have been documented. Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation.

Bacteriological response at the follow-up visit and clinical responses at the test-of-cure and follow-up visits were considered secondary variables. Bacteriological response at the follow-up visit was graded as continued eradication, persistence, superinfection, recurrence, new infection, or indeterminante. The following definitions are from the spnsor's study report.

Continued Eradication: Causative organism(s) present in numbers $<10^4$ CFU/mL at the test-of-cure and at late follow-up visits.
Persistence: Causative organism $\geq 10^4$ CFU/mL noted at the TOC visit regardless of the results of the culture at the follow-up visit, were carried forward.
Superinfection: Growth $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active study drug therapy, with symptoms of infection as previously stated.
Recurrence: Causative organism(s) in numbers $<10^4$ CFU/mL at the TOC, but reappearance of the same organism(s) $\geq 10^4$ CFU/mL before or at the Day +28 to +42 posttreatment visit.
New Infection: A pathogen other than the original microorganim isolated at baseline at a level of $\geq 10^5$ CFU/mL was present at a level $\geq 10^5$ CFU/mL anytime after treatment was finished.
Indeterminate: Bacteriological outcome could not be evaluated for any reason (eg, posttreatment culture was not obtainable). The reason for an indeterminate evaluation must have been documented.

Clinical outcome at the TOC visit was graded as clinical cure, clinical failure, or indeterminate. The following definitions are from the sponsor's study report.

Clinical Cure: Resolution or improvement of signs and symptoms at the TOC visit such that no additional antimicrobial therapy was administered or required.
Clinical Failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before the TOC visit, or the use of additional antimicrobial therapy was necessary for the current infection.
Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented. Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation.

Clinical outcome at the late follow-up visit was graded as continued clinical cure, failure, relapse, or indeterminate.

Continued Clinical Cure: Continued disappearance of acute signs and symptoms of infection or continued improvement such that alternative antimicrobial therapy was not required or administered.
Failure: An outcome of failure was carried forward from the TOC visit.
Relapse: Reappearance of signs and symptoms of the current infection considered to be related to an infectious (bacterial) process such that institution of alternative antimicrobial therapy was required.
Indeterminate: It was not possible to determine clinical outcome. The reason for indeterminate evaluation must have been documented.

As indicated above in the definitions of the endpoints, the protocol specified that subjects with an indeterminate evaluation at the TOC time point should be excluded from the efficacy analysis for that endpoint. The protocol did not specify how indeterminate responses at the follow-up visit would be handled for either the bacteriologic or clinical endpoints, however; in the study report, indeterminate responses at the follow-up visit were excluded from the analysis. By definition, the per-protocol analysis group excluded subjects, for whom the primary endpoint is not observed, in essence implementing the protocol-defined exclusion of subjects with indeterminate responses for the bacteriologic outcome at TOC. [Please see "Figure 1: Patient Disposition and Analysis Groups" for the frequency of exclusion due to "no TOC urine culture".] However, for the other endpoints (i.e., bacteriologic outcome at follow-up and clinical outcome at TOC and follow-up) the division commonly uses the established per-protocol analysis group and considers indeterminate responses for these endpoints failures. The analyses in this review will be conducted in accordance with this custom.

As per the 1998 draft FDA guidance, "Uncomplicated Urinary Tract Infection – Developing Antimicrobial Drugs for Treatment", the original protocol defined the timing of the test-of-cure visit to be within 5 and 9 days post-treatment and the timing of the follow-up visit to be within 28 and 42 days post-treatment. However, on August 30, 2002 (approximately 1.5 months after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 5 to 11 days post-treatment. The follow-up visit window was not modified. Under the newly amended time frame for the TOC visit, 17 subjects who previously were ineligible for the efficacy analysis at the TOC visit were now considered eligible for analysis. The study report does not indicate that this protocol amendment was made prior to data analysis and in fact states that the amendment was made since a number of patient visits occurred outside the protocol-specified TOC window, possibly indicating that examination of the efficacy data had begun. Further exploration of this issue is given in section *2.3.1.2*.

The primary efficacy objective of the study was to demonstrate non-inferiority of Cipro XR to Cipro® in terms of the bacteriological eradication rates at the TOC visit in patients with cUTI or AUP. A two-sided 95% confidence interval for the weighted difference between treatment groups was to be constructed, using Mantel-Haenszel weights (weighting by infection type). The difference was to be calculated as the proportion of subjects in the Cipro XR treatment group with eradication at the test-of-cure visit minus the same such proportion in the Cipro® group. Non-inferiority was defined as the lower limit of the two-sided 95% confidence interval for the difference between treatment groups being greater than –10%. Analysis of infection type by treatment interaction for the primary efficacy variable was planned using either the Breslow-Day test or Zelen's test.

The protocol-specified group that was to be used in the primary efficacy analysis was the per-protocol (PP) group defined as subjects meeting all of the following criteria.

- All inclusion/exclusion criteria were met;
- Study drug was given for a minimum of three days if the treatment result was failure, or a minimum of seven days if the treatment result was success;
- Bacteriological outcomes were determined at the TOC visit unless the patient's outcome was early treatment failure (patients with a response of Indeterminate at the TOC visit were invalid for the efficacy evaluation);
- No other systemic antibacterial agent was administered with the study drug during the study period up through the TOC visit unless the patient failed treatment;
- Adequate compliance must have been documented for each patient, with ≥80% of study medication taken;
- No protocol violation occurred during the course of therapy influencing treatment efficacy; and
- Study blind was not broken.

A modified intent-to-treat (mITT) analysis including all patients who received at least one dose of study drug and had a baseline pathogen was not protocol-specified but will be conducted by this reviewer. Patients with missing or indeterminate efficacy evaluations will be included and counted as nonsuccesses in all efficacy analyses carried out in the mITT population. While the PP efficacy results were designated in the protocol as the primary interest, it is division policy to consider the results of the mITT group of at least as much importance as that of the PP group for non-inferiority trials. Therefore this review will include discussion of the results from both analysis groups.

The protocol originally specified that 408 patients would be enrolled into the study. This sample size was calculated using the methods of Rodary[1], based on the previously described primary analysis methods using 90% power and the following assumptions.

- The true eradication rate for each treatment group is 83%,
- The smallest clinically meaningful difference between treatments (delta) is 15%, and
- The subject validity rate is 75%.

[1] Rodary C, Com-Nougue C, Tournade MF. How to establish equivalence between treatments: a one-sided clinical trial in pediatric oncology. *Stat Me*d. 1989;8:593-8.

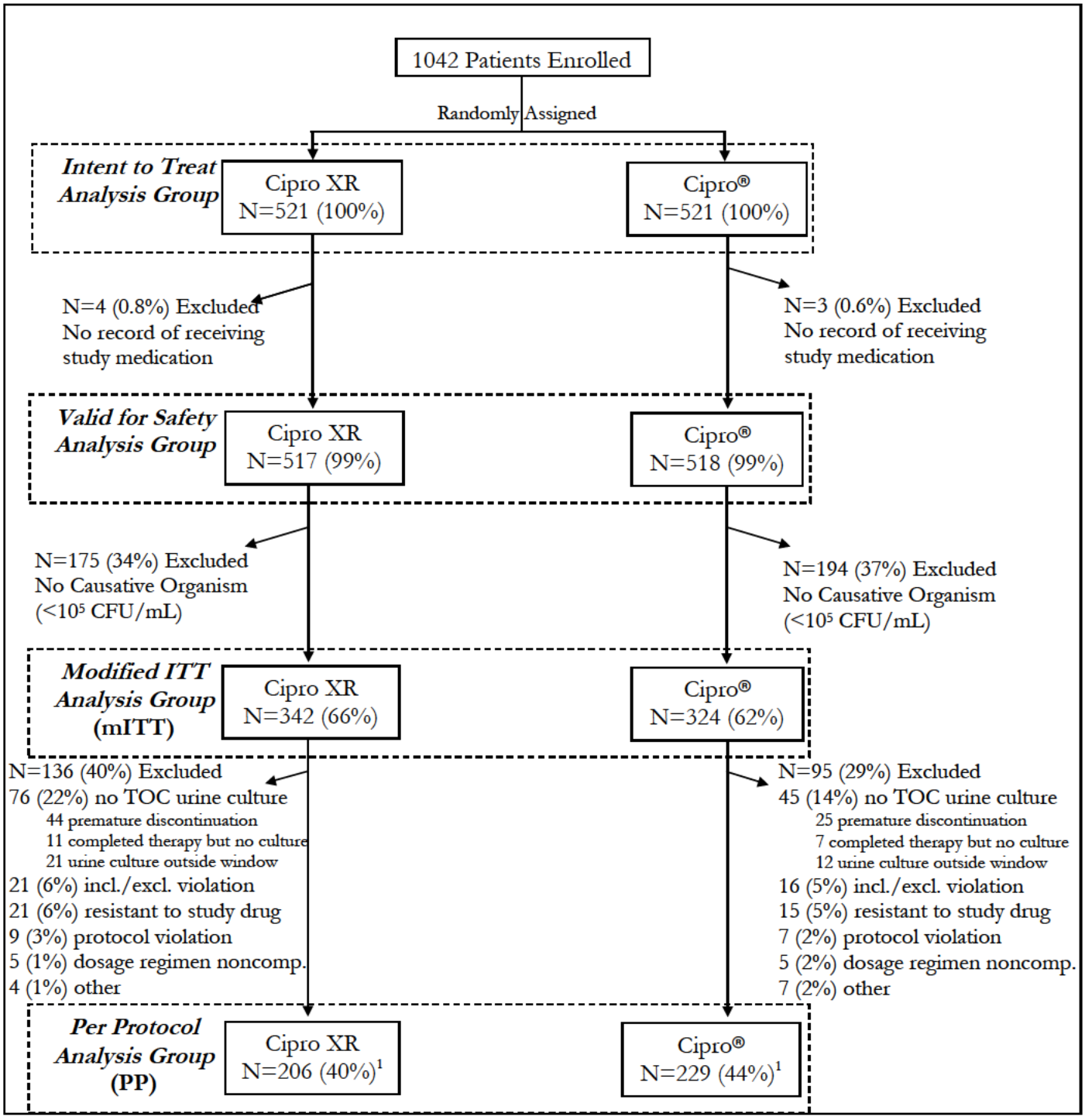
During the study, it became clear that the validity rate would be much lower than 75% because the rate of pretreatment urine culture results with $\geq 10^5$ CFU/mL of a causative organism was lower than originally anticipated. In addition, the observed eradication rate (88%) was higher than originally predicted (83%) and delta was adjusted from 15% to 10%. The protocol was amended three times to address these issues. First, approximately thirteen months after the finalization of the protocol the sample size was revised to reflect a delta of 10% (rather than 15%). This resulted in the need for 886 patients to be enrolled in order to obtain 664 valid patients. Approximately nine months later, the sample size calculation was revised again, this time to reflect an increase in the observed eradication rate (from 83% to 85%), decrease in power (from 90% to 85%), and decrease in the validity rate (from 75% to 50%). This resulted in the need for 948 patients to be enrolled in order to obtain the now necessary 474 valid patients. The third modification in the sample size calculation occurred approximately nine months later. This revision reflected an increase in the observed eradication rate (from 85% to 88%) and a decrease in the validity rate (from 50% to 39%). The result was that 1036 patients were needed to be enrolled to obtain the now necessary 404 valid patients. All of these sample size modifications were made prior to the study being unblinded and before any efficacy analyses were completed. Therefore it is the opinion of this reviewer that these sample size revisions in no way compromised the integrity of this study and no adjustment in the significance level (α) is warranted.

2.3.1.2 Results

The pivotal study enrolled 1042 patients at 100 centers. Five hundred twenty one were randomly assigned to treatment with Cipro XR and 521 were randomly assigned to treatment with Cipro®. Patient inclusion in and exclusion from the *intent-to-treat*, *valid for safety*, *modified intent-to-treat* (mITT), and *per-protocol* (PP) analysis data sets are described in Figure 1.

As indicated in Figure 1, seven subjects were excluded from the valid for safety analysis group, as there was no record of them receiving study medication. The only reason for further exclusions from the mITT analysis group in both treatments groups was no causative organism reported in a quantity $\geq 10^5$ CFU/mL. The Cipro® group had a slightly higher rate of patients (37%) with no causative organisms at a level $\geq 10^5$ CFU/mL compared with the Cipro XR group (34%). Further exclusions from the PP analysis group were made for the follow reasons; no TOC urine culture, violation of inclusion and/or exclusion criteria, organism resistant to study drug, protocol violation, noncompliance with the dosage regimen, and other (including inadequate duration of treatment, posttherapy antibiotics, and concomitant antimicrobial therapy). The Cipro XR group had a statistically significantly ($p=0.005$) higher rate (22%) of patients who had no valid TOC urine culture result compared to the Cipro® group (14%). This disproportionate exclusion is primarily due to subjects' premature discontinuation from the study and is of concern particularly since more patients in the experimental treatment group were affected. The most common reasons for premature discontinuation were protocol violation and adverse event. This may be an indication that some aspect of the effect of Cipro XR is causing patients to drop out. The rates of the other exclusions were similar between the two treatment groups.

Figure 1: Patient Disposition and Analysis Groups



1. Of these 206 Cipro XR subjects, 166 had cUTI and 40 had AUP. Of these 229 Cipro® subjects, 177 had cUTI and 52 had AUP.

Demographic and baseline variables (including causative orgainsm) for the PP and valid for safety analysis groups are summarized in Table 1. The weight, body mass index, and health status prior to study entry of Cipro XR subjects were statistically significantly different from those of the Cipro® subjects in the valid for safety analysis group. The means of weight and body-mass-index in the Cipro XR group were slightly lower than those measures in the Cipro® group. More Cipro XR subjects were given a health status rating of "excellent" than were Cipro® subjects. As would be expected since the PP analysis group is a subset of the valid for safety analysis group, trends in the PP analysis group were similar to the results in the valid for safety analysis group. However, these relationships were not statistically significant in the PP analysis group. Note that these endpoints (weight, body mass index, and health status) are likely correlated. These by-treatment imbalances may impact the efficacy and/or safety outcomes and should be kept in mind in interpreting the efficacy and safety results. Other than these variables, the distributions of the demographic and baseline variables were not statistically significantly different across treatment groups.

Examination of demographic and baseline variables by stratum revealed patterns similar to those described above, within each infection type (AUP and cUTI).

Table 1: Demographic and Baseline Variables Summary Statistics							
		PP Analysis Group			Safety Analysis Group		
		Cipro XR N=206[1]	Cipro® N=229[1]	By-trt. p-value[2]	Cipro XR N=517[1]	Cipro® N=518[1]	By-trt. p-value[2]
Age (years)	Mean (Median)	60.1 (66.0)	61.2 (66.0)	0.550	58.9 (63.0)	59.9 (65.0)	0.430
	Range	18.0 – 96.0	18.0 – 92.0		18.0 – 97.0	18.0 – 94.0	
Weight (kg)	Mean (Median)	75.8 (73.6)	78.3 (75.0)	0.213	75.1 (73.2)	77.6 (74.5)	0.041
	Range	43.6 – 129.1	50.0 – 156.8		39.1 – 150.0	44.5 – 174.3	
Body Mass Index	Mean (Median)	26.6 (26.0)	27.4 (26.0)	0.121	26.4 (26.0)	27.4 (26.0)	0.004
	Range	15.6 – 46.8	15.6 – 46.8		15.6 – 46.8	15.6 – 57.2	
Duration of Infection (days)	Mean (Median)	4.7 (3.0)	4.4 (3.0)	0.621	4.7 (3.0)	4.5 (3.0)	0.579
	Range	1.0 – 121.0	1.0 – 34.0		1.0 – 121.0	1.0 – 51.0	
Gender	Female	88 (43%)	102 (45%)	0.736	219 (42%)	219 (42%)	0.979
	Male	118 (57%)	127 (55%)		298 (58%)	299 (58%)	
Race	Caucasian	168 (82%)	177 (77%)	0.736	410 (79%)	414 (80%)	0.783
	Black	19 (9%)	27 (12%)		55 (11%)	48 (9%)	
	Asian	1 (<1%)	1 (<1%)		3 (<1%)	3 (<1%)	
	American Indian	0 (0%)	0 (0%)		1 (<1%)	0 (0%)	
	Hispanic	18 (9%)	24 (10%)		48 (9%)	53 (10%)	
Health Status Prior to Study Entry	Excellent	61 (30%)	43 (19%)	0.069	138 (27%)	100 (19%)	0.037
	Good	106 (51%)	135 (59%)		266 (51%)	302 (58%)	
	Fair	37 (18%)	49 (21%)		108 (21%)	110 (21%)	
	Poor	2 (<1%)	2 (<1%)		5 (<1%)	6 (1%)	
Infection Type	AUP	40 (19%)	52 (23%)	0.401	109 (21%)	111 (21%)	0.892
	cUTI	166 (81%)	177 (77%)		408 (79%)	407 (79%)	
Number of Underlying Conditions for cUTI	AUP	40 (19%)	52 (23%)	0.441	109 (21%)	111 (21%)	0.356
	Zero	0 (0%)	0 (0%)		8 (2%)	8 (2%)	
	One	119 (58%)	140 (61%)		283 (55%)	306 (59%)	
	Two	41 (20%)	33 (14%)		105 (20%)	86 (17%)	
	Three or more	6 (3%)	4 (2%)		12 (2%)	7 (1%)	
Pre-therapy Causative Organisms (subject may have ≥1 organism)	Acinetobacter Sp.	0	0	NA	0	1	NA
	Alcaligenes Xylosoxidans	0	0		0	1	
	Burkholderia Cepacia	1	0		3	0	
	Citrobacter Braakii	0	0		0	1	
	Citrobacter Freundii	4	4		4	5	
	Citrobacter Koseri	1	3		1	3	
	CitroBacter Youngae	1	0		1	0	
	Enterobacter Aerogenes	4	6		4	6	
	Enterobacter Cloacae	2	3		4	5	
	Enterococcus Faecalis	19	27		35	40	
	Enterococcus Faecium	2	0		3	2	
	Escherichia Coli	130	133		206	177	
	Klebsiella Oxytoca	1	7		3	9	
	Klebsiella Pneumoniae	25	25		40	36	
	Morganella Morganii	0	2		0	2	
	Proteus Mirabilis	12	14		16	17	
	Providencia Rettgeri	0	2		0	3	
	Providencia Stuartii	0	0		1	0	
	Pseudomonas Aeruginosa	4	3		9	6	
	Serratia Liquefaciens	0	0		0	1	
	Serratia Marcescens	2	4		2	5	
	Staphylococcus Aureus	6	4		8	8	
	Staphylococcus Saprophyticus	2	2		4	2	
	Weeksella Virosa	0	1		0	1	

1. Small amount of missing data (≤1%) for various endpoints was ignored.
2. P-values for categorical variables obtained using a chi-square test. P-values for continuous variables obtained using 1-way ANOVA.

Bacteriological response at the test-of-cure visit is the primary efficacy variable. The results for this endpoint in the overall group and in each of the strata (AUP and cUTI) are summarized in Table 2 for both the PP and mITT analysis groups.

Table 2

Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)

	PP Analysis Group		mITT Analysis Group	
	Cipro XR	**Cipro®**	**Cipro XR**	**Cipro®**
All Patients	**N=206**	**N=229**	**N=342**	**N=324**
Eradication	183 (88.8%)	195 (85.2%)	207 (60.5%)	214 (66.0%)
95% C. I. for Diff. in Prop. (weighted by infection type)	(-2.4%, 10.3%)* §		(-12.6%, 2.1%)§	
AUP Patients	**N=40**	**N=52**	**N=71**	**N=76**
Eradication	35 (87.5%)	51 (98.1%)	47 (66.2%)	58 (76.3%)
97.5% C. I. for Diff. in Prop.	(-34.8%, 6.2%)‡		(-26.8%, 6.5%)‡	
cUTI Patients	**N=166**	**N=177**	**N=271**	**N=248**
Eradication	148 (89.2%)	144 (81.4%)	160 (59.0%)	156 (62.9%)
97.5% C. I. for Diff. in Prop.	(-0.7%, 16.3%)‡		(-13.5%, 5.7%)‡	
Breslow-Day test for treatment-by-infection-type interaction in PP group, p-value=0.008				

*Sponsor's primary efficacy analysis.
§Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by infection type).
‡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.

The 95% confidence interval for the by-treatment difference in the proportions of subjects with eradication at the TOC visit (Cipro XR - Cipro®) in the PP analysis group excludes the protocol specified noninferiority margin of -10%. Under usual circumstances this along with similar results in the mITT analysis group, would lead to the conclusion that for this endpoint, Cipro XR is noninferior to Cipro®. However, in this case there is a statistically significant treatment-by-infection-type interaction (Breslow-Day test for interaction p-value = 0.008) indicating that the results of the treatment group comparisons between infection types were not consistent. In the PP analysis group, the eradication rates for the AUP subjects were higher in the Cipro® group (98.1%) than in the Cipro XR group (87.5%). Conversely, the eradication rates for the cUTI subjects were higher in the Cipro XR group (89.2%) than in the Cipro® group (81.4%). Such an interaction invalidates the results of the overall group, as the two strata should not be combined since the treatment effect is different for each stratum.

The sponsor suggests that the significance of the treatment-by-infection-type interaction is due to the fact that coincidentally three AUP patients in the Cipro XR group developed new infections while no AUP patients in the Cipro® group developed new infections. Given the sample size in the AUP stratum in each treatment group, the probability of three or more new infections occurring in the Cipro XR group and no new infections occurring in the Cipro® group by chance alone is less than 12%. For completeness, excerpts from the sponsor's study report describing the three cases of new infection are given below.

The first patient (62019) is a 21-year-old female with a medical history significant for urinary tract infection in 1999. She was not receiving any concomitant medications. The patient presented with 4 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mil/moderate signs and symptoms except for severe dysuria and back pain. Her temperature at study entry was 38.3^{O}C (orally), and the white blood cell (WBC) count was 9.7 x 10^9/L. Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro® XR 1000 mg QD, which she received for 10 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to 6.8 x 10^9/L. A repeat urine culture result at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* was identified in a quantity of $\geq 10^5$ CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient remained afebrile and her response was evaluated as continued clinical cure. Urine culture results revealed continued eradication of *E. coli* and absence of *E. faecalis*.

The second patient (82039) is a 19-year-old female with no significant medical history. Concomitant medications included acetaminophen and an oral contraceptive agent. The patient presented with 3 days of signs and symptoms of pyelonephritis, a temperature of 38.5^{O}C (orally), and a WBC count of 11.6 x 10^9/L. Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro® XR 1000 mg QD, which she received for 8 days. At the TOC visit, the patient's response was evaluated as clinical cure (no remaining signs or symptoms of infection). The WBC count had decreased to 6.4 x 10^9/L. A repeat urine culture result obtained at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* and *E. faecium* both were identified in a quantity of $\geq 10^5$ CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient's response was assessed as a continued clinical cure. Urine culture results at follow-up revealed continued eradication of *E. coli* and absence of both *Enterococcus* species.

The third patient (148023) is an 18-year-old female with no significant medical history, and she was not receiving any concomitant medications. The patient presented with 2 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mild/moderate signs and symptoms, a temperature of 38.8^{O}C (orally), and a WBC count of 9.7 x 10^9/L. Her pretherapy urine culture result was positive for *S. saprophyticus*, and she was assigned randomly to treatment with Cipro® XR 100 mg QD, which she received for 11 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to 5.5 x 10^9/L. A repeat urine culture result at the TOC visit was negative for *S. saprophyticus* (eradication); however, *E. faecalis* was identified in a quantity of $\geq 10^5$ CFU/mL (new infection). Alternative antibiotic therapy was prescribed (ciprofloxacin 500 mg BID for 7 days) 18 days following the completion of study drug therapy. At the post-alternative therapy visit the patient's clinical response was evaluated as clinical cure; there was no follow-up bacteriological evaluation.

Although perhaps implied by the clinical explanations given above, ultimately, the sponsor does not suggest that this data be reanalyzed while treating the three AUP patients in the Cipro XR group who developed new infections as successes. The explicit conclusion that the sponsor makes regarding the treatment-by-infection-type interaction is the following.

> "The results of the treatment group comparisons between infection types were not consistent… The p-value from the Breslow-Day test for treatment-by-infection-type interaction was 0.008, indicating that the treatment effect was different between pyelonephritis patients and complicated UTI patients."

This reviewer is in agreement with this conclusion.

The Division has considered post-hoc analyses aimed at eliminating the significance of the treatment-by-infection-type interaction. In particular an analysis considering the three patients described above as successes was conducted. Although this reassignment of

response did eliminate the significance of the interaction, in the opinion of this reviewer these types of analyses are not appropriate. The following description is given as statistical justification for why post-hoc reclassification of response is not appropriate.

Many post-hoc reclassifications schemes where a certain number of failures are considered successes could lead to a p-value for the treatment-by-infection-type interaction that is larger than α=0.10 (i.e., not statistically significant). There are five AUP subjects treated with Cipro XR who did not fall into the "eradication" category. And so as defined in the protocol were not considered successes. Reclassifying three, four, or five of these five failures, as successes would eliminate the significance of the interaction. There are several ways you can group the five failures into groups of size three. For simplicity suppose the subject numbers for the 5 failures are 1, 2, 3, 4, and 5. Then possible groups of size 3 are:

1, 2, 3	1, 3, 4	2, 3, 4	3, 4, 5
1, 2, 4	1, 3, 5	2, 3, 5	
1, 2, 5	1, 4, 5	2, 4, 5	

Mathematically this is described as "five choose three" and is written $\binom{5}{3}=10$, meaning that there are 10 ways to choose three of five patients. The number of ways you can group the 5 failures into groups of size 4:

1, 2, 3, 4	1, 3, 4, 5
1, 2, 3, 5	2, 3, 4, 5
1, 2, 4, 5	

In other words, $\binom{5}{4}=5$, meaning that there are 5 ways to choose four of five patients. Finally, there is one way to group the five failures into a group of 5. So in total there are 16 regroupings involving the AUP subjects treated with Cipro XR who were failures in the original analysis that would eliminate the significance of the treatment-by-infection-type interaction.

In addition, there are 33 cUTI subjects treated with Cipro® who did not fall into the "eradication" category and as per-protocol were not considered successes. Reclassifying 17 to 32 of these 33 failures as successes would eliminate the significance of the interaction. The number of ways you can regroup the 33 failures to remove the significance of the interaction test follows:

$\binom{33}{17}=1166803110$	$\binom{33}{21}=354817320$	$\binom{33}{25}=13884156$	$\binom{33}{29}=40920$
$\binom{33}{18}=1037158320$	$\binom{33}{22}=193536720$	$\binom{33}{26}=4272048$	$\binom{33}{30}=5456$
$\binom{33}{19}=818809200$	$\binom{33}{23}=92561040$	$\binom{33}{27}=1107568$	$\binom{33}{31}=528$
$\binom{33}{20}=573166440$	$\binom{33}{24}=38567100$	$\binom{33}{28}=237336$	$\binom{33}{32}=33$

So in total there are more than 4 billion regroupings involving the cUTI subjects treated with Cipro® who were failures in the original analysis that would eliminate the significance of the treatment-by-infection-type interaction.

The large number of possible reclassifications leading to an insignificant treatment-by-infection-type interaction illustrates the difficulties associated with post-hoc reassignment of response. As such, it is not surprising that out of more than 4 billion possible groupings, at least one can be portrayed as having clinically sound justification. From a statistical perspective, post-hoc reassignment of response and re-analyses are not appropriate. And conclusions should be drawn from the analysis of the subjects' responses as they were observed. The p-value from the Breslow-Day test for treatment-by-infection-type interaction using the observed data was 0.008, indicating that there is 0.8% chance of obtaining these results or something more extreme if no treatment-by-infection-type interaction exists. This is overwhelming statistical evidence that a treatment-by-infection-type interaction does exits. Such an interaction invalidates the results of the overall group, as the two strata should not be combined since the treatment effect is different for each stratum.

Since the random assignment of treatment was stratified by infection type, it is appropriate to consider the results of each stratum alone with an adjustment for multiple comparisons. Since no multiple comparison procedure was pre-specified, a Bonferroni correction has been implemented. Within the AUP stratum, the protocol-specified noninferiority criterion (exclusion of –10%) has not been met. In fact within the AUP stratum, Cipro XR appears to be worse than Cipro® for the eradication at TOC endpoint in the PP analysis group (as evidenced by the confidence interval for the by-treatment group difference being primarily below zero). Within the cUTI stratum, the protocol-specified noninferiority criterion (exclusion of –10%) is achieved. In fact within the cUTI stratum, Cipro XR is nearly statistically significantly better than Cipro® for the eradication at TOC endpoint in the PP analysis group (as evidenced by the confidence interval for the by-treatment group difference being nearly completely above zero). It is the opinion of this reviewer that Cipro XR has been shown to be noninferior to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group *within the cUTI stratum*. Noninferiority of Cipro XR to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group *in the AUP stratum* has not been demonstrated.

The mITT analysis group includes all subjects who had a baseline causative organism and received at least one dose of study medication. Thus this mITT analysis group includes the 136 (40%) Cipro XR subjects and 95 (29%) Cipro® subjects who were excluded from the PP analysis group (see Figure 1). Note that there were disproportionately and statistically significantly (p=0.004) more of these subjects in the Cipro XR group than in the Cipro® group (40% versus 29%). Subjects who are included in the mITT group but for whom the bacteriological response at TOC was missing or indeterminate were considered failures in this analysis. Similar patterns to that of the PP analysis group, were observed in the mITT analysis group for the AUP subjects (see Table 2). However, for the cUTI subjects, the pattern was different from the PP analysis group in that the eradication rate at TOC for

Cipro XR no longer appeared to be better than that of Cipro®. This may be a suggestion that the nearly statistically significantly superior result observed in the PP analysis group was an artifact of the disproportionate exclusion of more Cipro XR subjects than Cipro® subjects. In summary, for the mITT analysis, it is the opinion of this reviewer that the noninferiority of Cipro XR to Cipro® in terms of the bacteriological TOC endpoint has not been demonstrated within the AUP stratum. Within the cUTI group in the mITT analysis group, the noninferiority criterion is not met, as the lower bound of the 97.5% confidence interval for the by-treatment difference in proportions is -13.5%. The results do not indicate that Cipro XR is nearly statistically significant superior to Cipro® as was observed in the PP analysis group.

Bacteriological response at the follow-up was a secondary efficacy variable. The results for this endpoint in the overall group and in each of the strata (AUP and cUTI) are summarized in Tables 3a for both the PP and mITT analysis groups.

Table 3a

Bacteriologic Success at the Follow-up Time Point (Secondary Efficacy Endpoint)[†]

	PP Analysis Group		mITT Analysis Group	
	Cipro XR	**Cipro®**	**Cipro XR**	**Cipro®**
All Patients	**N=206**	**N=229**	**N=342**	**N=324**
Continued Eradication	124 (60.2%)	115 (50.2%)	146 (42.7%)	130 (40.1%)
95% C. I. For Diff. In Prop. (weighted by infection type)	(1.1%, 19.7%)[§]		(-4.5%, 10.4%)[§]	
AUP Patients	**N=40**	**N=52**	**N=71**	**N=76**
Continued Eradication	25 (62.5%)	35 (67.3%)	35 (49.3%)	41 (53.9%)
97.5% C. I. For Diff. In Prop.	(-27.3%, 17.7%)[‡]		(-23.1%, 13.8%)[‡]	
cUTI Patients	**N=166**	**N=177**	**N=271**	**N=248**
Continued Eradication	99 (59.6%)	80 (45.2%)	111 (41.0%)	89 (35.9%)
97.5% C. I. For Diff. In Prop.	(2.5%, 26.4%)[‡]		(-4.5%, 14.6%)[‡]	
Breslow-Day test for treatment-by-infection-type interaction in PP group, p-value=0.1047				

[§]Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by infection type).
[‡]Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation.
[†]Indeterminate responses were included and considered failures in this efficacy analysis.

In the PP analysis group, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro® group (67.3%) than in the Cipro XR group (62.5%). Conversely, the eradication rates for the cUTI subjects were higher in the Cipro XR group (59.6%) than in the Cipro® group (45.2%). Similar trends were observed in the mITT analysis group.

The trends in the bacteriologic endpoint at the follow-up visit are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata. The Breslow-Day test for interaction indicates that for the follow-up visit, there is a nearly statistically significant (α=0.01) treatment-by-infection-type interaction (p=0.1047). The replication of the same type of treatment-by-infection type interaction in

the bacteriologic endpoint at this time point is due in part to the fact that bacteriologic failures at the TOC visit were carried forward to the follow-up visit.

Clinical response at the TOC and follow-up visit were secondary efficacy variables. The results for these endpoints in the overall group and in each of the strata (AUP and cUTI) are summarized in Tables 3b for both the PP and mITT analysis groups.

Table 3b				
Clinical Success at the Test-of-Cure Time Point (Secondary Efficacy Endpoint)†				
	PP Analysis Group		**mITT Analysis Group**	
	Cipro XR	**Cipro®**	**Cipro XR**	**Cipro®**
All Patients	**N=206**	**N=229**	**N=342**	**N=324**
Clinical Cure	198 (96.1%)	211 (92.1%)	234 (68.4%)	240 (74.1%)
95% C. I. for Diff. in Prop. (weighted by infection type)	(-0.3%, 8.5%)§		(-12.5%, 13.0%)§	
AUP Patients	**N=40**	**N=52**	**N=71**	**N=76**
Clinical Cure	39 (97.5%)	50 (96.2%)	50 (70.4%)	58 (76.3%)
97.5% C. I. for Diff. in Prop.	(-15.3%, 21.1%)‡		(-22.0%, 10.4%)‡	
cUTI Patients	**N=166**	**N=177**	**N=271**	**N=248**
Clinical Cure	159 (95.8%)	161 (91.0%)	184 (67.9%)	182 (73.4%)
97.5% C. I. for Diff. in Prop.	(-1.1%, 10.8%)‡		(-14.4%, 3.5%)‡	
Clinical Success at the Follow-up Time Point (Secondary Efficacy Endpoint)*				
	PP Analysis Group		**mITT Analysis Group**	
	Cipro XR	**Cipro®**	**Cipro XR**	**Cipro®**
All Patients	**N=206**	**N=229**	**N=342**	**N=324**
Continued Clinical Cure	150 (72.8%)	151 (65.9%)	179 (52.3%)	173 (53.4%)
95% C. I. for Diff. in Prop. (weighted by infection type)	(-1.4%, 15.9%)§		(-8.3%, 6.8%)§	
AUP Patients	**N=40**	**N=52**	**N=71**	**N=76**
Continued Clinical Cure	30 (75.0%)	42 (80.8%)	40 (56.3%)	50 (65.8%)
97.5% C. I. for Diff. in Prop.	(-25.4%, 13.9%)‡		(-27.4%, 8.5%)‡	
cUTI Patients	**N=166**	**N=177**	**N=271**	**N=248**
Continued Clinical Cure	120 (72.3%)	109 (61.6%)	139 (51.3%)	123 (49.6%)
97.5% C. I. for Diff. in Prop.	(-0.6%, 22.0%)‡		(-8.2%, 11.5%)‡	

§Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by infection type).
‡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.
†Indeterminate responses were included and considered failures in this efficacy analysis.

In the PP analysis group, the clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro® and Cipro XR groups (97.5% and 96.2%, respectively). The clinical success rates for the cUTI subjects were slightly higher in the Cipro XR group (95.8%) than in the Cipro® group (91.0%).

In the PP analysis group, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR (75.0%) group than in the Cipro® group (80.8%). Conversely, the clinical success rates for the cUTI subjects were slightly higher in the Cipro XR group (72.3%) than in the Cipro® group (61.6%). These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint. The p-value for the Breslow-Day test for interaction for the clinical endpoint at follow-up is 0.1367.

The original protocol defined the timing of the test-of-cure visit to be within 5 and 9 days post-treatment and the timing of the follow-up visit to be within 28 and 42 days post-treatment. However, on August 30, 2002 (approximately 1.5 months after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 5 to 11 days post-treatment. The follow-up visit window was not modified. Under the newly amended time frame for the TOC visit, 17 subjects who previously were ineligible for the efficacy analysis at the TOC visit were now considered eligible for analysis. The study report does not indicate that this protocol amendment was made prior to data analysis and in fact states that the amendment was made since a number of patient visits occurred outside the protocol-specified TOC window, possibly indicating that examination of the efficacy data had begun. This reviewer conducted the analyses of the primary endpoint in adherence with the original protocol, i.e., including only the subjects with a test-of-cure visit within the protocol-defined test-of-cure window. The qualitative conclusions from this analysis are not different from those made above (see Table 2) where the amended TOC time frame is used. This provides reassurance that the results of the above analysis likely were not an artifact of the newly defined time frames. The results of the original protocol-defined analysis are summarized in Table 4.

Table 4*

Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)

	PP Analysis Group	
	Cipro XR	**Cipro®**
All Patients	**N=197**	**N=221**
Eradication	176 (89.3%)	188 (85.1%)
95% C. I. for Diff. in Prop. (weighted by infection type)	(-1.9%, 10.9%)	
AUP Patients	**N=39**	**N=50**
Eradication	34 (87.2%)	49 (98.0%)
97.5% C. I. for Diff. in Prop.	(-35.8%, 6.5%)	
cUTI Patients	**N=158**	**N=171**
Eradication	142 (89.9%)	139 (81.3%)
97.5% C. I. for Diff. in Prop.	(0.01%, 17.2%)	
Breslow-Day test for treatment-by-infection-type interaction in PP group, p-value=0.006		

* Analysis groups defined according to original-protocol-defined TOC time window of within 5 and 9 days post-treatment.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 5 displays the bacteriological response at the TOC time point by demographic variables.

Table 5: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Age and Race				
	PP Analysis Group			
	AUP Patients		CUTI Patients	
Eradication Rate	Cipro XR	Cipro®	Cipro XR	Cipro®
All Patients	35/40 (88%)	51/52 (98%)	148/166 (89%)	144/177 (81%)
Age				
<65 years	30/34 (88%)	49/50 (98%)	55/66 (83%)	41/57 (72%)
65 to 74 years	4/5 (80%)	0/0 (NA)	38/39 (97%)	40/49 (82%)
≥75 years	1/1 (100%)	2/2 (100%)	55/61 (90%)	63/71 (89%)
Race				
Caucasian	20/24 (83%)	27/28 (96%)	128/144 (89%)	122/149 (82%)
Black	6/6 (100%)	8/8 (100%)	11/13 (85%)	14/19 (74%)
Asian	1/1 (100%)	0/0 (NA)	0/0 (NA)	1/1 (100%)
Hispanic	8/9 (89%)	16/16 (100%)	9/9 (100%)	7/8 (88%)
Gender				
Male	6/7 (86%)	9/9 (100%)	75/81 (93%)	72/93 (77%)
Female	29/33 (88%)	42/43 (98%)	73/85 (86%)	72/84 (86%)

In general, the difference between treatment groups within each demographic subcategory mirrors the trend observed for the primary efficacy analysis in the overall group. That is the Cipro XR group has a higher eradication rate than Cipro® within cUTI subjects and conversely, the Cipro® group has a higher eradication rate than Cipro XR within AUP subjects.

Since the treatment effect appears to be different for each infection type, the by-treatment group differences in eradication rates are considered within each stratum. The differences in eradication rates in AUP subjects between the two treatment groups were difficult to judge because of the small number of subjects in each subcategory but appeared to be fairly constant across age, race, and gender subcategories. In cUTI subjects, the difference in eradication rates between the two treatment groups was greatest in the age group 65 to 74 years (97% Cipro XR and 82% Cipro®). The differences in eradication rates in cUTI subjects between the two treatment groups were fairly constant across race. In cUTI subjects, the difference in eradication rates between the two treatment groups was largest for males (93% Cipro XR and 77% Cipro®).

Table 6 displays the bacteriological response at the TOC time point by organism and strata. The eradication rates appear to be numerically similar in the two treatment groups for each of the organisms.

Table 6: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Organism		
	PP Analysis Group	
Eradication Rate in AUP Patients	**Cipro XR**	**Cipro®**
Staphylococcus Aureus	0/0 (NA)	1/1 (100%)
Staphylococcus Saprophyticus	1/1 (100%)	1/1 (100%)
Enterococcus Faecalis	0/1 (0%)	5/6 (83%)
Escherichia Coli	35/36 (97%)	41/41 (100%)
Klebsiella Pheumoniae	2/2 (100%)	2/2 (100%)
Proteus Mirabilis	0/0 (NA)	3/3 (100%)
Citrobacter Koseri	0/0 (NA)	1/1 (100%)
Pseudomonas Aeruginosa	1/1 (100%)	0/0 (NA)
Weeksella Virosa	0/0 (NA)	1/1 (100%)
Eradication Rate in cUTI Patients	**Cipro XR**	**Cipro®**
Staphylococcus Aureus	4/6 (67%)	2/3 (67%)
Staphyloicoccus Saprophyticus	1/1 (100%)	1/1 (100%)
Enterococcus Faecalis	17/18 (94%)	14/21 (67%)
Enterococcus Faecium	1/2 (50%)	0/0 (NA)
Escherichia Coli	91/94 (97%)	90/92 (98%)
Klebsiella Pneumoniae	20/23 (87%)	19/23 (83%)
Klebsiella Oxytoca	1/1 (100%)	6/7 (86%)
Proteus Mirabilis	11/12 (92%)	10/11 (91%)
Enterobacter Cloacae	2/2 (100%)	3/3 (100%)
Enterobacter Aerogenes	4/4 (100%)	6/6 (100%)
Serratia Marcescens	2/2 (100%)	4/4 (100%)
Citrobacter Freundii	3/4 (75%)	4/4 (100%)
Citrobacter Koseri	1/1 (100%)	1/2 (50%)
Citrobacter Youngae	1/1 (100%)	0/0 (NA)
Morganella Morganii	0/0 (NA)	2/2 (100%)
Providencia Rettgeri	0/0 (NA)	2/2 (100%)
Pseudomonas Aeruginosa	3/3 (100%)	3/3 (100%)
Burkholderia Cepacia	1/1 (100%)	0/0 (NA)

2.5 STATISTICAL AND TECHNICAL ISSUES

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Consideration of "indeterminate" bacteriologic or clinical responses at TOC or follow-up (ref: *Section 2.3.1.1*)
- Redefinition of acceptable time window for collection of TOC efficacy data (ref: *Section 2.3.1.1 and 2.3.1.2*)
- Sample size revisions as a result of overestimating the validity rate, under estimating the eradication rate, and changing delta from 15% to 10% (ref: *Section 2.3.1.1*)
- Statistically significant treatment-by-infection-type interaction for primary efficacy endpoint (ref: *Section 2.3.1.2*)

- Statistically significantly more subjects excluded from PP analysis group for Cipro XR group than Cipro® group (ref: *Section 2.3.1.2*)

2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

For this study, the results of the treatment group comparisons of the primary efficacy endpoint (i.e., bacteriologic outcome at TOC) between infection types were not consistent. A treatment-by-infection-type interaction was observed indicating that the treatment effect is different between AUP patients and cUTI patients and as such these two strata should be considered separately.

Within the cUTI stratum, it is the opinion of this reviewer that Cipro XR has been shown to be noninferior to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group. Disproportionately more subjects in the Cipro XR arm were excluded from the PP analysis group for no valid TOC urine culture (which most commonly was due to adverse event or protocol violation). The majority of these subjects were considered failures in the mITT analysis since their bacteriological response at TOC was likely missing or indeterminate. Within the cUTI stratum in the mITT group, the noninferiority criterion was not met.

Within the AUP stratum, it is the opinion of this reviewer that noninferiority of Cipro XR to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group has not been demonstrated. In fact within the AUP stratum, Cipro XR appears to be worse than Cipro® for the eradication at TOC endpoint in the PP analysis group. A similar trend is observed in the mITT group for this endpoint.

These results for the primary endpoint within each of the strata are not dependent on the use of the amended TOC window rather than the one defined in the original protocol.

Secondary endpoints for this study included the bacteriological response at follow-up and clinical responses at TOC and follow-up.

- The eradication rates at follow-up for the cUTI subjects were higher in the Cipro XR group than in the Cipro® group. Conversly, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro® group than in the Cipro XR group. These trends are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata.
- The clinical success rates at TOC for the cUTI subjects in the PP analysis group were slightly higher in the Cipro XR group than in the Cipro® group. The clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro® and Cipro XR groups in the PP analysis group. The Cipro XR group had slightly lower clinical success rates than the Cipro® group in the mITT analysis.
- The clinical success rates at the follow-up visit for the cUTI subjects in the PP analysis group were higher in the Cipro XR group than in the Cipro® group. Conversely, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR group than in the Cipro® group in the PP analysis group. Similar trends were

observed in the mITT analysis. These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint.

Examination of the primary efficacy endpoint by age, race, and gender indicated that in cUTI subjects, the difference in eradication rates between the two treatment groups was greatest in the age group 65 to 74 years. Also for cUTI subjects, the differences in eradication rates were fairly constant across races. And the difference in eradication rates was larger for males than females in cUTI subjects. The differences in eradication rates in AUP subjects between the two treatment groups were difficult to judge because of the small number of subjects in each subcategory but appeared to be fairly constant across age, race, and gender subcategories.

Tabulations of the bacteriologic success at the TOC visit were fairly numerically consistent across treatment groups for each of the organisms studied.

2.7 CONCLUSIONS AND RECOMMENDATIONS

It is the opinion of this reviewer that Cipro XR has been shown to be non-inferior to Cipro® in terms of the bacteriologic endpoint at TOC in cUTI subjects. Noninferiority of Cipro XR in comparison to Cipro® in terms of the bacteriologic endpoint at TOC within AUP subjects has not been demonstrated.

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/s/

Ruth Davi
7/28/03 02:14:43 PM
BIOMETRICS

Karen Higgins
7/28/03 03:15:39 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDAs #: 21-554

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 29-OCT-02
CDER DATE: 29-OCT-02
REVIEW ASSIGN DATE: 30-OCT-02
REVIEW COMPLETE DATE: 10-MAR-03

SPONSOR:
Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON:
Andrew S. Verderame
Director, Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Original New Drug Application (CIPRO® XR)

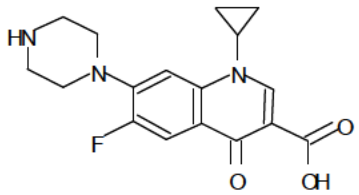
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Complicated Urinary Tract Infections

DOSAGE FORM: 1000-mg Tablets

DRUG PRODUCT NAME

PROPRIETARY: CIPRO® XR
NONPROPRIETARY/USAN: ciprofloxacin hydrochloride
CODE: BAY q 3939
CHEMICAL NAME: 1-cyclopropyl-6-fluoro-1,4-didydro-4-oxo-7[1-piperazinyl]-3-quinolone-carboxylic acid
STRUCTURAL FORMULA:



Molecular Formula: $C_{17}H_{18}FN_3O_3$
Molecular Weight: 331.4

SUPPORTING DOCUMENTS:

IND #21,804—Bayer Ciprofloxacin Tablets
IND #43,007—Bayer Ciprofloxacin Oral Suspension
IND #25,173—Bayer Ciprofloxacin IV
NDA #19-537—Bayer Ciprofloxacin Tablets—Approved October 22, 1987
NDA #19-847—Bayer Ciprofloxacin IV 1%--Approved December 26, 1990
NDA #19-857—Bayer Ciprofloxacin IV in 5% Dextrose—Approved December 26, 1990
NDA #19-858—Bayer Ciprofloxacin IV in 0.9% Saline—Approved December 26, 1990
NDA #20-780—Bayer Ciprofloxacin Oral Suspension—Approved September 26, 1997
NDA #21-473—Bayer Ciprofloxacin XR Tablets (500 mg)—Approved December 13, 2002

BACKGROUND:

This application is for a new dosage (1000 mg) extended release tablet of ciprofloxacin. This new formulation is a once daily (b) (4) tablet. This application requests indications of complicated urinary tract infections and acute uncomplicated pyelonephritis. The 500 mg extended release tablet formulation was approved in December, 2002 for uncomplicated urinary tract infections.

These ciprofloxacin extended release tablets are coated, two layer tablets containing both immediate-release and controlled-release components. Approximately 35% of the dose is provided by the immediate-release component and 65% by the slow-release matrix. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). The (b) (4) tablets result in a higher C_{max} and an equivalent AUC when compared to Cipro® Tablets for the same total dose (e.g. Ciprofloxacin XR 1000 mg tablets compared to Cipro® 500 mg twice daily).

This application is for the indications of complicated urinary tract infections and acute uncomplicated pyelonephritis. One randomized, double-blind, controlled multicenter clinical trial (Study 100275) forms the basis of the clinical section of the application. This trial was performed in patients with complicated urinary tract infections and acute uncomplicated pyelonephritis and enrolled 1,042 patients. This trial compared ciprofloxacin XR 1000 mg tablets given once a day for 7 to 14 days with Cipro® 500 mg tablets given twice a day for 7 to 14 days.

CONCLUSIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The required microbiology revisions are listed as recommendations at the end of this review on pages 23-26.

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EXECUTIVE SUMMARY

The applicant is requesting an indication of complicated urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis,* (b) (4)*,* or *Pseudomonas aeruginosa* and uncomplicated acute pyelonephritis caused by *Escherichia coli.*

In Study 100275 CIPRO (b) (4) tablets (1000 mg once daily for 7-14 days) were compared with immediate-release ciprofloxacin tablets (500 mg twice daily for 7-14 days) in the treatment of complicated urinary tract infections or acute uncomplicated pyelonephritis. The primary endpoint was bacteriological eradication at 5-11 days post-therapy. The bacteriological eradication rate for CIPRO XR in acute uncomplicated pyelonephritis (AUP) was 87.5% (35/40) compared to 98.1% (51/52) for immediate release tablets. The bacteriological rate for CIPRO XR in complicated UTI was 89.2% (148/166) compared to 81.4% (144/177) for the immediate release tablets. The eradication rates for individual pathogens are shown in TABLE A.

TABLE A
Bacteriological Eradication Rates at Test-of-Cure Visit

Pathogen	CIPRO XR (1000 mg QD)	Cipro Immediate Release (500 mg BID)
AUP Patients		
Escherichia coli	35/36 (97%)	41/41 (100%)
cUTI Patients		
Escherichia coli	91/94 (97%)	90/92 (98%)
Klebsiella pneumoniae	20/21 (95%)	19/23 (83%)
Enterococcus faecalis	17/17 (100%)	14/21 (67%)
Proteus mirabilis	11/12 (92%)	10/10 (100%)
Enterobacter aerogenes	4/4 (100%)	6/6 (100%)
Pseudomonas aeruginosa	3/3 (100%)	3/3 (100%)

As usual in urinary tract infections, most of the pathogens were *Escherichia coli.* There were very few of the other pathogens detected in the clinical trial. Eradication rates were good for all six of the listed pathogens. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa.*

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

No new information has been submitted.

IN VITRO ACTIVITY AGAINST RECENT CLINICAL ISOLATES FROM UTIs

SURVEILLANCE STUDIES

The (b) (4) (b) (4) provided national surveillance data for UTI isolates for the year 2001. More than 250 medical centers contributed to this database. TABLE 1 summarizes the *in vitro* activity of ciprofloxacin against the most common UTI pathogens during this time period.

TABLE 2
Ciprofloxacin Surveillance Data for UTI Isolates (b) (4)

Organism	Total Number	% Susceptible	% Intermediate	% Resistant
Citrobacter koseri	2,947	98.0	0.1	1.9
Citrobacter freundii	4,377	85.3	2.5	12.2
Enterobacter aerogenes	**3,843**	**95.7**	**0.6**	**3.7**
Enterobacter cloacae	5,224	85.1	1.7	13.2
Escherichia coli	**168,887**	**94.7**	**0.1**	**5.2**
Klebsiella oxytoca	3,348	91.5	1.3	7.2
Klebsiella pneumoniae	**28,181**	**95.3**	**0.6**	**4.2**
Proteus mirabilis	**16,871**	**84.5**	**1.3**	**14.2**
Serratia marcescens	1,743	84.6	3.2	12.2
Pseudomonas aeruginosa	**15,271**	**58.6**	**2.9**	**38.5**
Enterococcus faecalis	**11,872**	**61.4**	**5.4**	**33.2**
Staphylococcus aureus (MS)	3,523	81.9	1.4	16.7
Staphylococcus saprophyticus	826	98.7	0.2	1.1

MS = methicillin-susceptible
Bolded organisms are the ones proposed by the sponsor for the requested indication.

Over 90% of *Enterobacter aerogenes, Escherichia coli,* and *Klebsiella pneumoniae* isolates were susceptible to ciprofloxacin. Over 14% of *Proteus mirabilis* were resistant to ciprofloxacin. Over 30% of *Enterococcus faecalis* and *Pseudomonas aeruginosa* isolates were resistant to ciprofloxacin. *Enterococcus faecalis* is one of the organism listed under UTI in the present ciprofloxacin tablet label. It is listed in the microbiology subsection of the present ciprofloxacin tablet label with the qualifier that many strains are only moderately susceptible. This same qualifier is proposed for the labeling of this product. The percentages in the above table are based on breakpoints established for systemic infections. The amount

of ciprofloxacin in urine is much higher than in plasma, so ciprofloxacin should be effective in urinary tract infections against organisms that would appear to be resistant using these breakpoints.

An evaluation of the susceptibility of *Escherichia coli* in the nine U.S. Census regions showed that the susceptibility was similar in six of the nine regions; the susceptiblity rate was 95.6% to 98% (TABLE 2). In the Mid Atlantic, South Atlantic, and West South Central regions, the ciprofloxacin susceptibility of *E. coli* was somewhat lower at 91.4% to 92.5%.

TABLE 2
Ciprofloxacin Surveillance Data for *E. coli* UTI Isolates /2001/By Region*

Organism	Total Number	% Susceptible	% Intermediate	% Resistant
East North Central	27,674	96.0	0.1	3.9
East South Central	7,878	95.9	0	4.0
Mid Atlantic	24,188	92.3	0.1	7.6
Mountain	29,009	96.7	0.1	3.2
New England	3,739	98.0	0.1	2.0
Pacific	36,553	95.6	0.1	4.4
South Atlantic	21,267	91.4	0.2	8.4
West North Central	10,177	96.7	0	3.2
West South Central	10.820	92.5	0.1	7.4

(b) (4) (b) (4)

It appears that the overall susceptibility to ciprofloxacin has decreased after 15 years of use; however, the majority of the organisms responsible for most complicated urinary tract infections remain susceptible to ciprofloxacin, especially when urine concentrations of the drug are considered.

DATA FROM THE CLINICAL STUDY

This application has one pivotal study 100275. This was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter trial to evaluate the efficacy and safety of Cipro XR tablets, 1000 mg once daily for 7 to 14 days. The comparative arm was a conventional immediate-release ciprofloxacin 500-mg tablet twice daily for 7 to 14 days. The trial was for the treatment of patients with complicated urinary tract infections (cUTI) or acute uncomplicated pyelonephritis (AUP). The primary endpoint for this clinical trial was bacteriological eradication at the test-of-cure visit (5 to 11 days after the completion of therapy). Secondary efficacy parameters were microbiological outcome at the late follow-up visit (Day 28 to 42) and clinical outcome at both visits.

During the clinical study the susceptibility of the causative organisms was determined at the central laboratory (b) (4) Broth microdilution susceptibility tests were performed according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines. All causative organisms valid for efficacy from the Ciprofloxacin XR arm and ciprofloxacin immediate-release arm are listed in TABLE 3. *Escherichia coli* was the most frequently isolated organism (n=263), followed by *Klebsiella pneumoniae* (n=50), *Enterococcus faecalis* (n=46), and *Proteus mirabilis* (n=26). The MIC_{90} for *E. coli* was 0.06 μg/mL, while the MIC_{90} for *K. pneumoniae* and *P. mirabilis* were 0.5 μg/mL and 2 μg/mL, respectively. The MIC_{90} for the other 46 isolates of Enterobacteriaceae was $\leq$1 μg/mL and the MIC_{90} for *E. faecalis* was 2 μg/mL.

TABLE 3
MICs of Pre- therapy Isolates in Ciprofloxacin XR and Cipro Immediate-Release Arms
(Patients Valid for Efficacy)

Organism	Total Number	Range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Urine				
Staphylococcus aureus	10	0.12-2.0	0.25	0.5
Staphylococcus saprophyticus	4	0.12-0.25	0.25	0.25
Enterococcus faecalis	**46**	**0.25-2.0**	**1.0**	**2.0**
Enterococcus faecium	2	1.0-2.0	1.0	2.0
Escherichia coli	**263**	**0.008-1.0**	**0.015**	**0.06**
Klebsiella pneumoniae	**50**	**0.015-1.0**	**0.06**	**0.5**
Klebsiella oxytoca	8	0.015-0.5	0.015	0.5
Proteus mirabilis	**26**	**0.015-2.0**	**0.03**	**2.0**
Enterobacter cloacae	8	0.015-0.03	0.03	0.03
Enterobacter aerogenes	**10**	**0.015-0.25**	**0.03**	**0.06**
Serratia marcescens	6	0.06-1.0	0.06	1.0
Citrobacter freundii	8	0.008-0.12	0.015	0.12
Citrobacter koseri	4	0.008-0.5	0.008	0.5
Citrobacter youngae	1	0.015	0.015	0.015
Morganella morganii	2	0.015-0.015	0.015	0.015
Providencia rettgeri	2	0.03-0.03	0.03	0.03
Pseudomonas aeruginosa	**7**	**0.03-0.5**	**0.12**	**0.5**
Burkholderia cepacia	1	1.0	1.0	1.0
Weeksella virosa	1	1.0	1.0	1.0
Blood				
Escherichia coli	**11**	**0.015-0.25**	**0.015**	**0.12**
Klebsiella pneumoniae	**1**	**0.03**	**0.03**	**0.03**

TABLE 4 provides pre-therapy MIC data for all organisms isolated during the clinical trial for all patients valid for safety. The frequency of isolation of the organisms was about the same as that seen in the valid for efficacy population. The MIC_{90} for 383 isolates of *Escherichia coli* was 0.25 μg/mL, while the MIC_{90} for *K. pneumoniae* (n=76) and *P. mirabilis* (n=33) were 0.5 μg/mL and 2 μg/mL, respectively. The MIC_{90} for the majority of other Enterobacteriaceae (n=49) were $\leq$0.5 μg/mL with the exception of *Serratia marcescens* (n=7) which had a MIC_{90} of 16 μg/mL. The MIC_{90} for 75 isolates of *E. faecalis* was 16 μg/mL. The MIC_{90} for 15 isolates of *P. aeruginosa* was also 16 μg/mL.

TABLE 4
MICs of Pre- therapy Isolates in Ciprofloxacin XR and Cipro Immediate-Release Arms
(Patients Valid for Safety)

Organism	Total Number	Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Urine				
Staphylococcus aureus	16	0.12-16.0	0.5	16.0
Staphylococcus saprophyticus	6	0.12-0.25	0.25	0.25
Enterococcus faecalis	**75**	**0.25-16.0**	**1.0**	**16.0**
Enterococcus faecium	5	1.0-16.0	16.0	16.0
Escherichia coli	**383**	**0.008-16.0**	**0.015**	**0.25**
Klebsiella pneumoniae	**76**	**0.015-16.0**	**0.03**	**0.5**
Klebsiella oxytoca	12	0.015-0.5	0.03	0.06
Proteus mirabilis	**33**	**0.015-16.0**	**0.03**	**2.0**
Enterobacter cloacae	9	0.015-0.03	0.03	0.03
Enterobacter aerogenes	**10**	**0.015-0.25**	**0.03**	**0.06**
Serratia marcescens	7	0.06-16.0	0.06	16.0
Serratia liquefaciens	1	0.03	0.03	0.03
Citrobacter freundii	9	0.008-0.5	0.06	0.5
Citrobacter koseri	4	0.008-0.5	0.008	0.5
Citrobacter youngae	1	0.015	0.015	0.015
Citrobacter brakii	1	0.015	0.015	0.015
Morganella morganii	2	0.015-0.015	0.015	0.015
Providencia stuartii	1	4.0	4.0	4.0
Providencia rettgeri	2	0.03-0.03	0.03	0.03
Pseudomonas aeruginosa	**15**	**0.03-16.0**	**0.25**	**16.0**
Burkholderia cepacia	3	0.12-8.0	1.0	8.0
Acinetobacter species	1	4.0	4.0	4.0
Acinetobacter xylosoxidans	1	4.0	4.0	4.0
Weeksella virosa	1	1.0	1.0	1.0
Blood				
Staphylococcus aureus	1	0.12	0.12	0.12
Staphylococcus saprophyticus	1	0.25	0.25	0.25
Enterococcus faecalis	**1**	**0.5**	**0.5**	**0.5**
Escherichia coli	**22**	**0.008-16.0**	**0.025**	**0.12**
Klebsiella pneumoniae	**2**	**0.03-0.06**	**0.03**	**0.06**
Acinetobacter species	2	0.25-0.5	0.25	0.5

PHARMACOKINETICS/BIOAVAILABILITY

The proposed dose is a single 1000-mg tablet taken once a day for 7 to 14 days.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following 1000 mg Ciprofloxacin XR once daily is 16.83 mg.h/L. This is about equal to the AUC for immediate-release ciprofloxacin 500 mg given twice daily. The peak plasma concentration (C_{max}) of Ciprofloxacin XR 1000 mg is higher than that seen with the corresponding Ciprofloxacin 500 mg immediate-release tablet. Median time to maximum plasma concentration (t_{max}) for Ciprofloxacin XR was 2.0 hours, which was comparable to that of immediate-release ciprofloxacin. The elimination half-lives for both formulations were approximately six hours. TABLE 4 compares the pharmacokinetic parameters at steady state for the two tablet formulations.

TABLE 4
Ciprofloxacin Pharmacokinetics (Mean ± Standard Deviation)

	C_{max} (µg/mL)	AUC_{0-24h} (mg.h/L)	$T_{1/2}$ (hours)	T_{max} (hours)*
CIPRO XR 1000 mg QD	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1-4)
CIPRO 500 mg BID	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5-3.5)

* median (range)

RESULTS FROM CLINICAL TRIAL

STUDY 100275

This was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter trial to evaluate the efficacy and safety of Cipro XR tablets, 1000 mg once daily for 7 to 14 days. The comparative arm was a conventional immediate-release ciprofloxacin 500-mg tablet twice daily for 7 to 14 days. The trial was for the treatment of patients with complicated urinary tract infections (cUTI) or acute uncomplicated pyelonephritis (AUP). The primary endpoint for this clinical trial was bacteriological eradication at the test-of-cure visit (5 to 11 days after the completion of therapy). Secondary efficacy parameters were microbiological outcome at the late follow-up visit (Day 28 to 42) and clinical outcome at both visits.

A total of 1042 patients were enrolled at 100 centers in the US and Canada. Of the 1042 enrolled patients, 521 were assigned to treatment with Cipro XR 1000 mg QD and 521 were assigned to treatment with Cipro 500 mg BID. Seven patients (4 in the Cipro XR group and 3 in the Cipro 500 mg BID group) were not included in the valid for safety population because study drug administration could not be documented. There were 517 (408 cUTI and 109 pyelonephritis) patients in the Cipro XR QD group and 518 (407 cUTI and 111 pyelonephritis) patients in the Cipro 500 mg BID group in the valid for safety population.

TABLE 5 displays the reasons for premature termination of the study. As seen in this table, 199 patients in the Cipro XR group and 91 patients in the Cipro BID group did not complete the study as planned. The most common reason for discontinuation was a protocol violation. The most common protocol violations were lack of causative organisms (i.e. no pretherapy pathogen recovered, organism recovered at $<10^5$ CFU/mL, or no urine culture specimen obtained) or the presence of a resistant organism.

TABLE 5
Reasons for premature discontinuation of study drug

	Cipro XR (N = 521)	Cipro BID (N =521)
Any reason	119 (23%)	91 (17%)
Adverse Event	28 (5%)	20 (4%)
Patient non-compliance	8 (2%)	7 (1%)
Consent withdrawn	9 (2%)	11 (2%)
Insufficient therapeutic effect	7 (1%)	4 (<1%)
Patient lost to follow-up	17 (3%)	13 (2%)
Death	2 (1%)	0 (0%)
Protocol violation	48 (9%)	36 (7%)

TABLE 6 presents a summary of the reasons for patients being excluded from the efficacy population.

TABLE 6
Reasons for exclusion from the efficacy population

	Cipro XR (N = 521)	Cipro BID (N =521)
Any reason	315 (61%)	292 (56%)
No causative organism	175 (34%)	194 (37%)
No valid test-of-cure urine culture	76 (15%)	45 (9%)
Exclusion/inclusion criteria violation	21 (4%)	16 (3%)
Organism resistant to study drug	21 (4%)	15 (3%)
Protocol violation	9 (2%)	7 (1%)
Noncompliance with dosage regimen	5 (1%)	5 (1%)
Did not receive study drug	4 (1%)	3 (1%)
Inadequate duration of treatment	1 (0%)	4 (1%)
Posttherapy antibiotics	2 (<1%)	2 (<1%)
Concomitant antimicrobial therapy	1 (<1%)	1 (<1%)
Valid for efficacy	206 (39.5%)	229 (44%)

The Cipro BID group had a slightly higher rate of patients who had no causative organism. The Cipro XR group had a higher rate (15%) of patients who had no valid test-of-cure (TOC) urine culture result as compared to the Cipro BID group (9%). There were, therefore, four hundred thirty-five patients valid for efficacy—206 (166 cUTI; 40 AUP) in the Cipro XR group and 229 (177 cUTI; 52 AUP) in the Cipro BID group. TABLE 7 summarizes the microbiological outcome for the valid for efficacy patients at the TOC visit.

TABLE 7
Microbiological Outcome at the Test-of-Cure Visit
(Valid for Efficacy Population)

	Ciprofloxacin XR 1000 mg PO QD x 7-14 days	Cipro® 500 mg PO BID x 7-14 days
All Patients	N = 206	N = 229
Eradication (%)	183 (88.8%)	195 (85.2%)
Persistence (%)	10 (4.9%)	17 (7.4%)
Superinfection (%)	5 (2.4%)	3 (1.3%)
New Infection (%)	8 (3.9%)	14 (6.1%)
AUP Patients	N = 40	N = 52
Eradication (%)	35 (87.5%)	51 (98.1%)
Persistence (%)	2 (5.0%)	1 (1.9%)
New Infection (%)	3 (7.5%)	0
cUTI Patients	N = 166	N = 177
Eradication (%)	148 (89.2%)	144 (81.4%)
Persistence (%)	8 (4.8%)	16 (9.0%)
Superinfection (%)	5 (3.0%)	3 (1.7%)
New Infection (%)	5 (3.0%)	14 (7.9%)

When all patients are considered the eradication rates for Cipro XR and Cipro BID are about equal. The results of the treatment group comparisons between infection types were not consistent. Whereas the eradication rates for pyelonephritis patients was higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%), they were higher in the Cipro XR group (89.2%) than in the Cipro BID group (81.4%) in complicated UTI patients. The difference between patients with pyelonephritis and those with complicated UTI was caused primarily by the outcome of three pyelonephritis patients in the Cipro XR group who developed a new infection compared to zero patients in the Cipro BID group. All three cases of new infection were females between the ages of 18 and 21 years. All of the new infections were due to *Enterococcus faecalis* or *Enterococcus faecalis* and *Enterococcus faecium.* All three patients had a clinical response of cure at the TOC visit and only one patient had alternative treatment. All organisms were eradicated at the follow-up visit.

Results for the microbiological outcome at the late follow-up visit are summarized in TABLE 8.

TABLE 8
Microbiological Outcome at the Late Follow-Up Visit
(Valid for Efficacy Population)

	Ciprofloxacin XR 1000 mg PO QD x 7-14 days	Cipro® 500 mg PO BID x 7-14 days
All Patients	N = 206	N = 229
Continued Eradication	124 (60.2%)	115 (50.2%)
Eradication with Recurrence	19 (9.2%)	18 (7.9%)
Persistence	10 (4.9%)	17 (7.4%)
Superinfection	5 (2.4%)	2 (0.9%)
New Infection	21 (10.2%)	36 (15.7%)
Indeterminate	27 (13.1%)	41 (17.9%)
Continued Eradication Rate[a]	124/179 (69.3%)	115 /188 (61.2%)
AUP Patients	N = 40	N = 52
Continued Eradication	25 (62.5%)	35 (67.3%)
Eradication with Recurrence	1 (2.5%)	3 (5.8%)
Persistence	2 (5.0%)	1 (1.9%)
New Infection	5 (12.5%)	4 (7.7%)
Indeterminate	7 (17.5%)	9 (17.3%)
Continued Eradication Rate[a]	25/33 (75.8%)	35/43 (81.4%)
CUTI Patients	N = 166	N = 177
Continued Eradication	99 (59.6%)	80 (45.2%)
Eradication with Recurrence	18 (10.8%)	15 (8.5%)
Persistence	8 (4.8%)	16 (9.0%)
Superinfection	5 (3.0%)	2 (1.1%)
New Infection	16 (9.6%)	32 (18.1%)
Indeterminate	20 (12.0%)	32 (18.1%)
Continued Eradication Rate[a]	99/146 (67.8%)	80/145 (55.2%)

[a] Continued Eradication rates do not include indeterminate responses

The Cipro XR group had a higher rate of continued eradication and lower rates of persistence and new infections, the Cipro BID group had a lower rate of superinfection. The rate of eradication with recurrence was similar in the two groups. Among patients with pyelonephritis, the continued eradication rate (not including indeterminate responses) was 76% (25/33) in the Cipro XR group and 81% (35/43) in the Cipro BID group. There was a higher rate of eradication with recurrence in the Cipro BID group (5.8%, as compared with 2.5% in the Cipro XR group), and more patients in this group than in the Cipro XR group developed a new infection during the follow-up period (2 in the Cipro XR group and 4 in the Cipro BID group).

TABLE 9 shows the microbiological results by pathogen at the TOC visit for the organisms proposed for this indication in the label.

TABLE 9
Bacteriological Eradication Rates at Test-of-Cure
(Patients Valid for Efficacy)

Organism	Cipro XR			Cipro BID		
	Erad (%)	Pers (%)	Indeter (%)	Erad (%)	Pers (%)	Indeter (%)
AUP Patients						
Escherichia coli	35 (97%)	1 (3%)	0	41 (100%)	0	0
cUTI Patients						
Escherichia coli	91 (97%)	3 (3%)	0	90 (98%)	2 (2%)	0
Klebsiella pneumoniae	20 (87%)	1 (4%)	2 (9%)	19 (83%)	4 (17%)	0
Enterococcus faecalis	17 (94%)	0	1 (6%)	14 (67%)	7 (33%)	0
Proteus mirabilis	11 (92%)	1 (8%)	0	10 (91%)	0	1 (9%)
Enterobacter aerogenes	4 (100%)	0	0	6 (100%)	0	0
Pseudomonas aeruginosa	3 (100%)	0	0	3 (100%)	0	0
Blood						
AUP Patients						
Escherichia coli	4 (80%)	0	1 (20%)	3 (75%)	0	1 (25%)
Klebsiella pneumoniae	1 (100%)	0	0	0	0	0
cUTI Patients						
Escherichia coli	1 (100%)	0	0	1 (100%)	0	0

Erad = eradication; Pers = persistence; Indeter = Indeterminate

The eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. Eradication rates for *Escherichia coli*, by far the most common organism, were high for both treatment groups. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*.

TABLE 10 presents a summary of the organisms causing superinfections or new infections in patients valid for efficacy. In the Cipro XR group, 5 patients had organisms that caused superinfections and 8 patients had organisms that caused new infection. In the Cipro BID group, 3 patients had organisms that caused superinfection and 14 patients had organisms that caused new infection. *Enterococcus faecalis* was the organism causing new infection in 7 patients in the Cipro XR group and 6 patients in the Cipro BID group. *Staphylococcus aureus* was the organism causing superinfection in the 3 patients in the Cipro XR group and new infection in 1 patient in the Cipro XR group and 4 patients in the Cipro BID group.

TABLE 10
Organisms Causing Superinfections or New Infections at TOC
(Patients Valid for Efficacy)

Organism	Cipro XR	Cipro BID
Superinfection		
Staphylococcus aureus	3	0
Enterococcus faecalis	0	1
Klebsiella pneumoniae	0	1
Pseudomonas aeruginosa	2	1
Alcaligenes faecalis	0	1
New Infection		
Staphylococcus aureus	1	4
Enterococcus species	0	1
Enterococcus faecalis	7	6
Enterococcus faecium	1	0
Escherichia coli	0	1
Proteus mirabilis	0	1
Citrobacter freundii	0	1
Providencia stuartii	1	0
Acinetobacter calcoaceticus	0	1
Comamonas testosterone	1	0

The number of organisms causing super or new infection is higher than patients with bacteriological response of super or new infection; this is due to some patients having persisting organisms and super or new infections. The patient response for these patients is persistence, but the super or new infecting organism is still shown in this table.

TABLE 11 presents the bacteriological response rates by pathogen at the follow-up visit for the organisms proposed for this indication in the label.

TABLE 11
Bacteriological Eradication Rates at Follow-up (28 to 42 days posttreatment)
(Patients Valid for Efficacy)

Organism	Cipro XR				Cipro BID			
	Erad (%)	Recurr (%)	Pers (%)	Indeter (%)	Erad (%)	Recurr (%)	Pers (%)	Indeter (%)
AUP Patients								
Escherichia coli	27 (75%)	0	1 (3%)	8 (22%)	33 (80%)	1 (2%)	0	7 (17%)
cUTI Patients								
Escherichia coli	74 (79%)	10 (11%)	3 (3%)	7 (7%)	60 (65%)	10 (11%)	2 (2%)	20 (22%)
Klebsiella pneumoniae	13 (57%)	2 (9%)	1 (4%)	7 (30%)	12 (52%)	0	4 (17%)	7 (30%)
Enterococcus faecalis	10 (56%)	2 (11%)	0	6 (33%)	7 (33%)	2 (10%)	7 (33%)	5 (24%)
Proteus mirabilis	9 (75%)	1 (8%)	1 (8%)	1 (8%)	6 (55%)	2 (18%)	0	3 (27%)
Enterobacter aerogenes	3 (75%)	0	0	1 (25%)	3 (50%)	0	0	3 (50%)
Pseudomonas aeruginosa	1 (33%)	1 (33%)	0	1 (33%)	1 (33%)	1 (33%)	0	1 (33%)
Blood								
AUP Patients								
Escherichia coli	4 (80%)	0	0	1 (20%)	3 (75%)	0	0	1 (25%)
Klebsiella pneumoniae	1 (100%)	0	0	0	0	0	0	0
cUTI Patients								
Escherichia coli	1 (100%)	0	0	0	1 (100%)	0	0	0

Erad = continued eradication; Recurr = eradication with recurrence; Pers = persistence;
Indeter = Indeterminate

The eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*.

Organisms isolated at the follow-up visit that caused new infections in patients valid for efficacy are presented in TABLE 12. Of the 39 new infecting organisms recovered after the test-of-cure (TOC) visit, 18 were identified as *Enterococcus faecalis* (7 from patients in the Cipro XR group and 11 from patients in the Cipro BID group), 7 were identified as *Escherichia coli* (4 and 3, respectively), and 7 were identified as *Klebsiella pneumoniae* (0 and 7, respectively). There were more patients in the Cipro BID group than in the Cipro XR group who had new infecting organisms isolated between the TOC and follow-up visits (17 in the Cipro XR group versus 26 in the Cipro BID group).

TABLE 12
Organisms Causing New Infections at Follow-Up (after TOC Visit)
(Patients Valid for Efficacy)

Organism	Cipro XR	Cipro BID
New Infection		
Staphylococcus aureus	2	0
Staphylococcus saprophyticus	1	0
Enterococcus species	0	1
Enterococcus faecalis	7	11
Escherichia coli	4	3
Klebsiella pneumoniae	0	7
Klebsiella oxytoca	1	0
Citrobacter freundii	1	1
Citrobacter amalonaticus	0	1
Pseudomonas aeruginosa	1	2

The number of organisms causing super or new infection is higher than patients with bacteriological response of super or new infection; this is due to some patients having persisting organisms and super or new infections. The patient response for these patients is persistence, but the super or new infecting organism is still shown in this table.

Four hundred twenty-nine of the 435 valid for efficacy patients had a pretherapy blood culture obtained. Twelve of these 429 patients had bacteremia caused by *E. coli* (11 patients) and *K. pneumoniae* (1 patient). Ten of the twelve patients had subsequent blood cultures performed at the during-therapy visit; blood cultures were missing for the remaining two bacteremic patients. The infecting organism in the blood was eradicated in all 10 of the 12 patients who had blood culture results. These blood isolates are included in TABLEs 13 and 14.

TABLE 13 shows the bacteriological response for the acute pyelonephritis patients by MIC value. TABLE 14 shows the same data for the complicated urinary tract infection patients (cUTI). Persistence was not associated with elevated MICs for any of the organisms.

TABLE 13
Microbiological Responses by MIC—AUP Patients (Patients Valid for Efficacy)

Organism	MIC (μg/mL)	Outcome	Ciprofloxacin (b)(4) 500 mg QD		Ciprofloxacin 250 mg BID	
			Number	%	Number	%
AUP Patients—Urine						
Escherichia coli	0.008	Eradication	1	100	3	100
	0.015	Eradication	24	96	25	100
		Persistence	1	4	0	0
	0.03	Eradication	6	100	7	100
	0.06	Eradication	2	100	2	100
	0.12	Eradication	1	100	1	100
	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	2	100
	ALL	Eradication	35	97	41	100
		Persistence	1	3	0	0
AUP Patients--Blood						
Escherichia coli	0.015	Eradication	4	80	0	0
		Indeterminate	1	20	1	100
	0.03	Eradication	0	0	1	100
	0.12	Eradication	0	0	1	100
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	80	3	75
		Indeterminate	1	20	1	25
Klebsiella pneumoniae	0.03	Eradication	1	100	0	0
	ALL	Eradication	1	100	0	0

TABLE 14
Microbiological Responses by MIC—cUTI Patients (Patients Valid for Efficacy)

cUTI Patients--Urine						
Escherichia coli	0.008	Eradication	10	100	6	100
	0.015	Eradication	54	98	50	98
		Persistence	1	2	1	2
	0.03	Eradication	19	100	24	100
	0.06	Eradication	4	80	3	100
		Persistence	1	20	0	0
	0.12	Eradication	0	0	5	100
	0.25	Eradication	2	100	1	50
		Persistence	0	0	1	50
	0.5	Eradication	2	67	0	0
		Persistence	1	33	0	0
	1.0	Eradication	0	0	1	100
	ALL	Eradication	91	97	90	98
		Persistence	3	3	2	2
Enterococcus faecalis	0.25	Eradication	0	0	1	50
		Persistence	0	0	1	50
	0.5	Eradication	6	100	3	50
		Persistence	0	0	3	50
	1	Eradication	11	100	8	89
		Persistence	0	0	1	11
	2	Eradication	0	0	2	50
		Persistence	0	0	2	50
		Indeterminate	1	100	0	0
	ALL	Eradication	17	94	14	67
		Persistence	0	0	7	33
		Indeterminate	1	6	0	0
Klebsiella pneumoniae	0.015	Eradication	1	100	1	100
	0.03	Eradication	4	67	10	83
		Persistence	0	0	2	17
		Indeterminate	2	33	0	0
	0.06	Eradication	5	83	4	67
		Persistence	1	17	2	33
	0.12	Eradication	2	100	1	100
	0.25	Eradication	4	100	0	0
	0.5	Eradication	2	100	2	100
	1.0	Eradication	2	100	1	100
	ALL	Eradication	20	87	19	83
		Persistence	1	4	4	17
		Indeterminate	2	9	0	0

TABLE 14 (Continued)
Microbiological Responses by MIC—cUTI Patients (Patients Valid for Efficacy)

Organism	MIC (μg/mL)	Outcome	Ciprofloxacin (b) (4) 500 mg QD		Ciprofloxacin 250 mg BID	
			Number	%	Number	%
Proteus mirabilis	0.015	Eradication	2	100	0	0
	0.03	Eradication	5	100	5	100
	0.06	Eradication	3	75	1	100
		Persistence	1	25	0	0
	0.12	Eradication	0	0	1	100
	0.5	Indeterminate	0	0	1	100
	1	Eradication	1	100	0	0
	2	Eradication	0	0	3	100
	ALL	Eradication	11	92	10	91
		Persistence	1	8	0	0
		Indeterminate	0	0	1	9
Enterobacter aerogenes	0.015	Eradication	1	100	1	100
	0.03	Eradication	1	100	4	100
	0.06	Eradication	2	100	0	0
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	100	6	100
Pseudomonas aeruginosa	0.12	Eradication	2	100	2	100
	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	0	0
	ALL	Eradication	3	100	3	100
cUTI Patients—Blood						
Escherichia coli	0.015	Eradication	1	100	0	0
	012	Eradication	0	0	1	100
	ALL	Eradication	1	100	1	100

The patients valid for efficacy who were bacteriological persisters or clinical failures are shown in TABLE 15. More bacteriological persisters and clinical failures were seen in the Cipro BID arm (n = 26) compared with the Cipro XR arm (n = 15).

TABLE 15
Patients with Bacteriological Persistence or Clinical Failure

Patient #	Treatment	Organism	Cipro MIC	Bact Resp At TOC	Bact Resp At FU	Clin Resp At TOC	Clin Resp At FU
15005	Cipro XR	*E. coli*	0.06	Persistence	Persistence	Cure	
31006	Cipro XR	*P. mirabilis*	0.06	Persistence	Persistence	Cure	Relapse
31012	Cipro XR	*E. faecalis*	1.0	Eradication	Indeterminate	Failure	Failure
42012	Cipro XR	*S. aureus*	2.0	Persistence	Persistence	Cure	
42056	Cipro XR	*C. freundii*	0.12	Persistence	Persistence	Failure	Failure
48037	Cipro XR	*S. aureus*	0.25	Persistence	Persistence	Cure	
49061	Cipro XR	*E. coli*	0.5	Persistence	Persistence	Cure	Con. Cure
73042	Cipro XR	*K. pneumoniae*	0.25	Eradication	Indeterminate	Failure	Failure
77018	Cipro XR	*E. coli*	0.015	Persistence	Persistence	Relapse	Relapse
98001	Cipro XR	*K. pneumoniae*	0.06	Persistence	Persistence	Cure	Failure
125006	Cipro XR	*K. pneumoniae*	0.25	Eradication	Indeterminate	Failure	Failure
127001	Cipro XR	*E. faecalis*	2.0	Indeterminate	Indeterminate	Failure	Failure
127001	Cipro XR	*K. pneumoniae*	0.03	Indeterminate	Indeterminate	Failure	Failure
209029	Cipro XR	*E. coli*	0.015	Persistence	Persistence	Cure	Relapse
209039	Cipro XR	*E. faecalis*	1.0	Persistence	Persistence	Failure	Failure
12002	Cipro BID	*E. coli*	0.015	Eradication	Indeterminate	Failure	Failure
13017	Cipro BID	*E. faecalis*	1.0	Persistence	Persistence	Cure	Con. Cure
15011	Cipro BID	*K. pneumoniae*	0.03	Persistence	Persistence	Cure	Relapse
25005	Cipro BID	*K. oxytoca*	0.5	Persistence	Persistence	Cure	Relapse
25029	Cipro BID	*E. faecalis*	1.0	Persistence	Persistence	Cure	Con. Cure
25029	Cipro BID	*E. coli*	0.03	Eradication	Con. Erad	Cure	Con. Cure
42038	Cipro BID	*C. koseri*	0.5	Persistence	Persistence	Cure	Failure
45019	Cipro Bid	*E. faecalis*	0.5	Persistence	Persistence		
48013	Cipro BID	*E. coli*	0.03	Eradication	Indeterminate	Failure	Failure
53029	Cipro BID	*K. pneumoniae*	0.06	Eradication	Persistence	Failure	Failure
59033	Cipro BID	*K. pneumoniae*	0.5	Eradication	Indeterminate	Failure	Failure
73046	Cipro BID	*E. faecalis*	0.25	Persistence	Persistence	Cure	Con. Cure
73046	Cipro BID	*E. coli*	0.015	Eradication	Con Erad	Cure	Con. Cure
74015	Cipro BID	*K. pneumoniae*	0.03	Persistence	Persistence	Failure	Failure
76011	Cipro BID	*K. pneumoniae*	0.06	Persistence	Persistence	Failure	Failure
77006	Cipro BID	*E. coli*	0.015	Persistence	Persistence		
91008	Cipro BID	*E. coli*	0.25	Persistence	Persistence	Failure	Failure
92011	Cipro BID	*E. faecalis*	1.0	Eradication	Indeterminate	Failure	Failure
92011	Cipro BID	*S. marcescens*	1.0	Eradication	Indeterminate	Failure	Failure
97001	Cipro BID	*S. aureus*	0.5	Persistence	Persistence	Relapse	Relapse
101007	Cipro BID	*E. faecalis*	2.0	Persistence	Persistence	Cure	
106019	Cipro BID	*K. pneumoniae*	0.03	Eradication	Indeterminate	Failure	Failure
127006	Cipro BID	*E. faecalis*	0.5	Persistence	Persistence	Failure	Failure
129001	Cipro BID	*E. faecalis*	2.0	Persistence	Persistence	Failure	Failure
133008	Cipro BID	*E. coli*	0.03	Eradication	Indeterminate	Failure	Failure
201006	Cipro BID	*E. faecalis*	0.5	Persistence	Persistence	Failure	Failure

Cipro = ciprofloxacin; Bact Resp = bacteriological response; Clin Resp = clinical response
TOC = test-of-cure; FU = follow-up
Con. Cure = continued cure; Con. Erad. = continued eradication

Isolates that had a MIC at post-therapy that was more than one dilution greater than the pretherapy MIC are presented in TABLE 16. Of 65 isolates from either the Cipro XR or Cipro BID arm, 11 isolates had elevated MICs at the Test-of-Cure (TOC) visit. The six isolates that were in the Cipro XR arm included *Escherichia coli* (n = 4), *Klebsiella pneumoniae* (n = 1), and *Staphylococcus aureus* (n = 1). The MICs of 2 isolates of *Escherichia coli* increased to 16 μg/mL; however, the organisms were eradicated at the TOC visit, but recurred at the follow-up visit. The MIC of one isolate of *E. coli* increased from 0.015 to 0.12 μg/mL and was not eradicated and the MIC of the other isolate, which recurred at the follow-up visit, increased from 0.03 to 0.5 μg/mL. The MIC of the isolate of *K. pneumoniae* increased from 0.06 to 0.5 μg/mL, while the MIC of the isolate of *S. aureus* increased from 2 to 16 μg/mL. Neither organism was eradicated. Similar results were seen in the Cipro BID arm. The development of resistance during therapy was low.

TABLE 16
Organisms with Elevated MICs (μg/mL) at Posttherapy[a]

Organism (No.)	MIC (μg/mL)		Eradication	
	Pre-Therapy	Post-Therapy	TOC	FU
Escherichia coli				
Cipro XR Arm (4)	0.015	0.12	No	No
	0.03	0.5	Yes	Recurred
	0.03	16	Yes	Recurred
	0.06	16	Yes	Recurred
Cipro BID Arm (3)	0.015	0.5	Yes	Recurred
	0.015	1.0	Yes	Recurred
	0.015	16	No	No
Enterococcus faecalis				
Cipro BID Arm (2)	0.5	2	No	No
	1	16	No	No
Klebsiella pneumoniae				
Cipro XR Arm (1)	0.06	0.5	No	No
Staphylococcus aureus				
Cipro XR Arm (1)	2	16	No	No

[a] MIC at post-therapy greater than one dilution higher than MIC at pre-therapy

LABELING

The Microbiology subsection of the proposed label closely follows the label for ciprofloxacin tablets. Only organisms indicated for UTI have been placed in the clinical and *in vitro* activity listing (list #1). List #2 (*in vitro* activity only) has organisms that are listed in the ciprofloxacin tablet label. All the Gram-negative microorganisms are appropriate since they may be associated with UTI infections. The applicant has also listed (b) (4) *and* (b) (4) These two Gram-positive organisms are usually not associated with UTI infections and should, therefore, be deleted.

The susceptibility testing section is basically identical to that in the ciprofloxacin tablet label, but has been amended to include only the sections pertinent to organisms that are indicated for UTI infections. The statement that introduces the interpretive criteria should be revised to state what organisms the criteria are for rather than what organisms the criteria are not appropriate for. The revised labeling, which should be sent to the applicant, is presented at the end of this review under RECOMMENDATIONS on pages 23-26.

RECOMMENDATIONS
(To Be Communicated to Sponsor)

The sponsor should be notified of the following:

1. (b) (4) should be deleted from the listing of organisms with *in vitro* activity (list #2). These organisms are not usually associated with UTI infections.

2. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa* in the clinical trial. The Medical Officer will have to decide whether enough evidence was presented to allow these organisms into the clinical efficacy listing (list #1). If allowed they should be listed in alphabetical order.

3. In the Susceptibility Tests subsection the two sentences that read (b) (4) should be revised to read "For testing (b) (4)

4. The (b) (4) should be deleted from both susceptibility testing sections unless this organism is allowed in the indications.

5. The following statement should be added to the Diffusion Techniques subsection: "Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for (b) (4)

6. The NCCLS references should be updated to the January 2003 versions.

The Microbiology subsection should, therefore, read as follows:
Proposed additions are double-underlined. Proposed deletions are indicated by a strikeout.

(b) (4)

2 page(s) has been Withheld in Full as draft labeling (CCI/TS) immediately following this page

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA # 21-554
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/JMeyer
HFD-590/BioPham/DChilukuri
HFD-520/Pharm/SHundley
HFD-590/Chem/DMatecka
HFD-590/CSO/JSaliba

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA	21-554
Generic	Ciprofloxacin
(Brand®)	CIPRO® XR
Dosage Strength	1000 mg
Submission Date	October 29, 2002
Applicant	Bayer
Clinical Division	DSPIDP (HFD-590)
OCPB Division	DPE3 (HFD-880)
Type of Submission	NDA original submission
Reviewer	Dakshina Chilukuri, Ph.D.
Pharmacometrics Reviewer	Jenny J. Zheng, Ph.D.
Team Leader	Philip Colangelo, Ph.D.
Review Date	July 11, 2003

EXECUTIVE SUMMARY

The applicant is seeking approval of CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin*) tablets containing 1000 mg ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration in NDA 21-554. CIPRO® XR Tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The proposed indications are treatment of complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, (b) (4), or *Pseudomonas aeruginosa* and acute uncomplicated Pyelonephritis caused by *Escherichia coli*. The dosage regimen for complicated urinary tract infection and acute uncomplicated Pyelonephritis is CIPRO XR 1000 mg once-daily for 7-14 days.

CIPRO® XR 1000 mg is a (b) (4) tablet formulation of ciprofloxacin. A lower strength of CIPRO® XR (500 mg) was approved in NDA 21-473 for the treatment of uncomplicated urinary tract infections (Acute Cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, or Staphylococcus saprophyticus.* Ciprofloxacin is bactericidal at concentrations only two to four-fold above its bacteriostatic concentrations. Its bactericidal action results from inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, which are enzymes required for bacterial DNA replication, transcription, repair and recombination.

CIPRO® XR tablets are coated, two-layer tablets containing both immediate- release and controlled-release components. Approximately 35% of the dose is provided by the immediate-release component and 65% by the slow-release matrix. The tablets contain both ciprofloxacin hydrochloride and ciprofloxacin betaine (base), and excipients that contribute to the desired characteristics of the formulation.

A total of 5 clinical pharmacology studies were conducted with CIPRO® XR 1000 mg in healthy volunteers. These studies compared pharmacokinetics of the CIPRO® XR 1000 mg once-daily regimen to the corresponding immediate release regimen (eg, 1000 mg XR vs. 500 mg immediate release BID) and examined the effects of food on the performance of the XR tablet. In addition, the drug interaction studies to study the effect of Maalox

and Omeprazole on the pharmacokinetics of CIPRO® XR were also conducted. These studies were reviewed in NDA 21-473 as part of the CIPRO® XR 500 mg tablet formulation.

The 24-hour area under the curve (AUC) obtained following administration of 1000 mg CIPRO® XR was shown to be equivalent to that attained with BID dosing of 500 mg immediate release ciprofloxacin. The bioavailability of the XR tablet was not altered by administration with food (either a high-fat or a low-fat meal), and did not change upon multiple dosing for 5 days. The C_{max} following administration of the 1000 mg XR tablet was higher than that observed for the 500 mg immediate release tablet. Trough plasma concentrations are lower with the 1000 mg XR once-daily regimen compared to the 500 mg BID regimen. However, urine concentrations of ciprofloxacin following dosing with 1000 mg CIPRO® XR are maintained well above (>100-fold) the *in vitro* MIC_{90} for *Escherichia coli* (about 0.03 µg/mL).

Dosage adjustments for patients with renal impairment based on the Monte-Carlo simulations are acceptable. Additional simulations are recommended to confirm the applicant's proposed dosage adjustments and are listed below.

Based on the efficacy and safety results, the medical officer recommends approval for the CIPRO® XR 1000 mg tablets.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in original NDA 21-554 for CIPRO® XR. The Human Pharmacokinetics and Bioavailability Section of NDA 21-554 has met the requirements of the 21 CFR 320 and the clinical pharmacology labeling requirements of 21 CFR 201.56.

Dissolution: Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method for the tablet (USP Apparatus 2, rotation speed of 50 rpm, and dissolution medium of 0.1N HCl), is acceptable. The acceptance criteria for dissolution proposed by the applicant are acceptable and are given below:

30 minutes: (b) (4)%
60 minutes: (b) (4)%
120 minutes: Not Less Than (b) (4)%

Dosage adjustments for renal impairment: Monte-Carlo simulations:

1. It appears the applicant used FO method in the modeling and simulation. It is known that FOCE/INTERACTION method is preferable for a relatively dense data set. Please address why only FO was used.

2. In the simulation, according to the code, CL_{cr} of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renally impaired and severely renal impaired, respectively. This approach is considered to be inadequate. It

is preferable to simulate with ranges of CL_{cr} values for normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment. Therefore, as a Phase IV commitment, please perform additional Monte-Carlo simulations to obtain estimates of ciprofloxacin systemic exposure after administration of the following regimens:

- 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
- 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4)-50 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4) 50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CL_{cr} (b) (4) 120 mL/min)

Based on the information obtained from the above-mentioned simulations, adjustments to the dosage regimen for CIPRO® XR 1000 mg in patients with mild and/or moderate renal impairment may be needed.

3. The applicant used the established relationship between clearance (CL) of intravenously administered ciprofloxacin and creatinine clearance (CL_{cr}). However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of the orally administered Cipro IR tablet and use it for the purpose of modeling and simulations. We recommend that the applicant re-develop the relationship between oral ciprofloxacin clearance and creatinine clearance (CL_{cr}) and compare with the previous results.

Labeling: The proposed label for ciprofloxacin XR tablets with the Clinical Pharmacology and Biopharmaceutics reviewer comments is attached as Appendix-1.

Phase IV commitments: The applicant is asked to address the following as Phase IV commitments:
Please perform additional Monte-Carlo simulations to obtain estimates of systemic exposure after administration of the following regimens:

- 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
- 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4) 50 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)

- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4) 50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CL_{cr} (b) (4) 120 mL/min)

Dakshina Chilukuri, Ph.D. _____
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Philip Colangelo, Ph.D. _____
cc: NDA 21-554, HFD-590, HFD-880 and CDR (Biopharm).

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SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Single-dose and steady-state pharmacokinetics of CIPRO 1000 mg XR tablet vs. 500 mg IR tablet

The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of the CIPRO 1000 mg XR formulation to healthy subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation. The PK parameters observed following administration of CIPRO XR 1000 mg were comparable to the parameters observed following administration of Cipro IR 500 mg bid.

Effect of food (pilot study) on pharmacokinetics of ciprofloxacin CIPRO 1000 mg XR tablet

The applicant compared the safety, tolerability and pharmacokinetics of the new CIPRO 1000 mg XR formulation given after a standard breakfast (4 slices toast, 20g butter, 50g jam, 20g cheese, 200mL decaffeinated coffee, 3g sugar) and after an overnight fast in comparison to the marketed immediate release ciprofloxacin product, given orally according to the bid dosing schedule as two doses of 500 mg to healthy subjects. After single dose administration of CIPRO 1000 mg XR ciprofloxacin tablet to fasted healthy subjects, the relative bioavailability (AUC_{0-24}) of ciprofloxacin was 96% and the 90% CI lay within the bioequivalence criteria compared with 500 mg bid IR tablet. However, C_{max} was significantly greater by 89% for the XR formulation compared to the 500 mg IR tablet. No effect of food on the exposure of ciprofloxacin was observed.

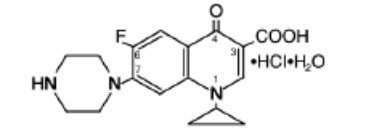
Effect of a high calorie, high fat meal on the pharmacokinetics of ciprofloxacin 1000 mg XR tablet

The applicant evaluated the effect of a high calorie, high fat meal (250 mL whole milk, 2 slices toast, 2 scrambled eggs, 3 slices fried ham, 125g hash brown potatoes, 20g butter and 2 cups decaffeinated coffee- providing a total of 977 Kcal) on the pharmacokinetics of CIPRO® XR 1000 mg formulation in healthy subjects. The CIPRO® XR formulation was found to be bioequivalent when administered under fasted and high fat, high calorie fed conditions. Hence, food does not appear to affect the rate or extent of ciprofloxacin exposure.

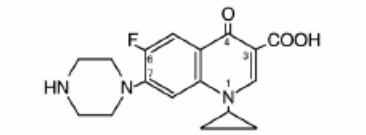
QUESTION BASED REVIEW
General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

CIPRO® XR tablets contain ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO® XR tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3- quinolinecarboxylic acid hydrochloride monohydrate. Its empirical formula is $C_{17}H_{18}FN_3O_3$ .HCl.H_2O and its molecular weight is 385.8. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7- (1- piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



The composition of the commercial tablet formulation is as follows:

Ingredient	**Amount (mg/tablet)**
IR -Layer	
Ciprofloxacin hydrochloride	(b) (4)
(b) (4) (Ciprofloxacin betaine)	
Crospovidone	
Magnesium stearate	
Silica colloidal anhydrous	
CR -Layer	
Ciprofloxacin hydrochloride	
(b) (4) (Ciprofloxacin betaine)	

(b) (4)		(b) (4)
Hypromellose		
Magnesium stearate		
Silica colloidal anhydrous		
Film Coat		
Hypromellose		
Polyethylene glycol		
Titanium dioxide		
Total Weight	1513 mg	

What is the proposed mechanism of drug action and therapeutic indications?
Ciprofloxacin is bactericidal at concentrations only two to fourfold above its bacteriostatic concentrations. Its bactericidal action results from inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, which are enzymes required for bacterial DNA replication, transcription, repair, and recombination.

What is the proposed dosage and route of administration?
In complicated urinary tract infections and in acute uncomplicated pyelonephritis, the recommended dosage of CIPRO® XR is 1000 mg once daily for 7-14 days.

What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data?
CIPRO XR (1000 mg once daily for 7 to 14 days) was evaluated for the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis in a large, randomized, double-blind, controlled clinical trial conducted in the US and Canada. This study compared CIPRO XR with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days) and enrolled 1,042 patients. The primary endpoint for this trial was bacteriological eradication at 5 to 11 days post-therapy for all patients evaluable for efficacy. The bacteriological eradication rate for CIPRO XR was 88.8% (183/206) compared to 85.2% (195/229) for immediate-release ciprofloxacin.

PATHOGEN	CIPRO XR 1000 mg QD	Immediate-Release Ciprofloxacin 500 mg BID
Escherichia coli	97% (91/94)	98% (90/92)
Klebsiella pneumoniae	95% (20/21)	83% (19/23)
Enterococcus faecalis	100% (17/17)	67% (14/21)
Proteus mirabilis	92% (11/12)	100% (10/10)
Enterobacter aerogenes	100% (4/4)	100% (6/6)
Pseudomonas aeruginosa	100% (3/3)	100% (3/3)

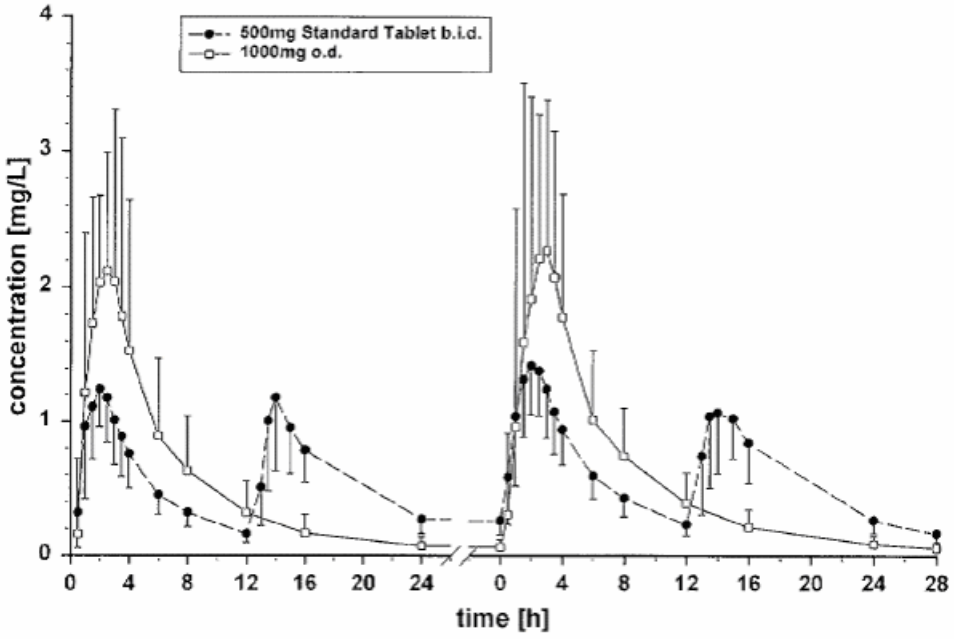
The clinical success rate in CIPRO XR treated patients with a diagnosis of complicated urinary tract infection was 96.4% (159/165) compared to 93.1% (161/173) in patients treated with immediate-release ciprofloxacin. The bacteriological eradication rates at the test-of-cure visit for the microbiologically evaluable patients with a diagnosis of acute

uncomplicated pyelonephritis caused by *Escherichia coli* was 97.2% (35/36) compared to 100.0% (41/41) in patients treated with immediate-release ciprofloxacin. Please refer to the medical officer's review for a more detailed discussion of safety and efficacy issues.

Do PK parameters change with time following chronic dosing?
The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new 1000 mg XR formulation to healthy male subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation.

The peak to trough (PTF) ratios were 4.02 for the CIPRO® XR formulation and was 2.65 for the IR formulation. The presence of an IR component in the CIPRO® XR product may be the cause for higher ratio.

Figure 11.5.2-1: Plasma concentration vs time curves for ciprofloxacin (BAY q 3939) including the geometric standard deviation in study 10324 (N=18)



How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
The plasma and urine drug concentration measurements were not obtained in patients and hence a comparison of the PK of healthy volunteers to patients cannot be made.

What are the basic PK parameters?
The PK parameters in healthy volunteers are given below:

Table 2-2 Ciprofloxacin steady state pharmacokinetics (Mean ± SD) following multiple (5 days) oral dose administration of Cipro® XR 1g once daily and conventional Cipro® 0.5g twice daily in healthy male subjects

	Study	N	Cmax (mg/L)	AUC (mg*h/L)	$T_{1/2}$ (hr)	T_{max} (hr)[a]
CIPRO XR 1g QD	10324	18	3.11 ±1.08	16.83 ±5.65	6.31 ±0.72	2.0 (1-4)
CIPRO 0.5g BID			2.06 ±0.41	17.04 ±4.79	5.66 ±0.89	2.0 (0.5-3.5)

[a]median (range)

What is the inter-individual variability of PK parameters in subjects?
The interindividual variability of the pharmacokinetic parameters of CIPRO XR was low (<30%) as known for ciprofloxacin and appeared comparable between the treatments.

Based upon what is known about exposure-response relationships and their variability, and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these subgroups?

a) Elderly
Pharmacokinetic studies of immediate-release Cipro Tablets (single dose) and intravenous ciprofloxacin (single and multiple dose) indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) compared to young adults. C_{max} is increased by 16% to 40%, and mean AUC is increased by approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant and no dosage adjustments for age alone (i.e., without renal impairment) is needed.

b) Pediatric patients
Safety and effectiveness of ciprofloxacin in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals.

c) Gender
No studies were conducted to study the effect of gender on the pharmacokinetics of CIPRO XR 1000 mg product.

d) Race
No studies were conducted to study the effect of race on the pharmacokinetics of CIPRO XR 1000 mg product.

e) Renal impairment

The applicant's proposal to reduce the dosage of CIPRO XR 1000 mg in patients with severe renal impairment to CIPRO XR 500 mg is acceptable. For patients with mild and moderate renal impairment, no dosage adjustments are recommended. As a Phase IV commitment, the applicant has been asked to perform additional Monte-Carlo simulations to characterize the exposure of CIPRO XR 1000 mg (administered QD for 14 days) in patients with mild and moderate renal impairment. Based on these results, changes in labeling may be recommended at a later time.

f) Hepatic impairment

No significant changes in the pharmacokinetics of ciprofloxacin have been observed in studies of patients with stable chronic cirrhosis of the liver. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. There is no difference in the proposed labeling for CIPRO® XR with respect to hepatic insufficiency from that of immediate- release ciprofloxacin. This proposal is acceptable.

g) What pregnancy and lactation use information is there in the application?

Reproduction studies were performed in rats and mice using oral doses of ciprofloxacin up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 mg/kg and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies any potential risk to the fetus. There were 7 pregnancies in Study 100346 (3 in the CIPRO® XR group and 4 in the Cipro 250 mg BID). Four of the pregnancies resulted in spontaneous abortions (2 in each group). There is one ongoing pregnancy in each of the two treatment groups as of the date of this summary. One patient in the Cipro 250 mg BID gave birth to a full-term infant via normal vaginal delivery during the study period. There were neither maternal complications nor infant abnormalities. The infant's Apgar score at 1 and 5 minutes was 8 and 9, respectively.

What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of aluminium and magnesium containing antacid and proton pump inhibitor, omeprazole, on the exposure of Cipro XR 1000 mg was previously evaluated during the review of Cipro XR 500 mg product. For details please refer to the biopharm review of the Cipro XR 500 mg product (NDA 21-473) by Dakshina Chilukuri. The recommendations for dosage adjustments of antacids and omeprazole are given below:

Maalox:
The rate of ciprofloxacin absorption was not affected by Maalox®. The extent of systemic absorption (AUC) was reduced by about 26% after co-administration of Maalox® given 2 hours before or 4 hours after ciprofloxacin administration. The amount of ciprofloxacin excreted into urine over 0-24 hours was not significantly decreased following pre-treatment with Maalox®, and urine concentrations exceeded the MIC_{90} for *E. coli* by at least 100-fold. CIPRO® XR can be administered at least 2 hours before or 6 hours after Maalox® is administered.

Omeprazole:
Omeprazole slightly reduced the rate and extent of ciprofloxacin exposure. The exposure of ciprofloxacin is decreased (20%) by pre-treatment with omeprazole compared with ciprofloxacin given alone. However, the amount of ciprofloxacin excreted in urine over 24 hours was not significantly different in the two groups. Moreover, ciprofloxacin urine concentrations in the omeprazole-treated group exceeded the MIC for *E. coli* by at least 100-fold throughout the proposed 24-hour dosing interval. It can be concluded that the decrease in ciprofloxacin plasma and urine concentrations observed with co-administration of omeprazole is not clinically significant for the treatment of uncomplicated UTI.

What is the effect of food on the bioavailability (BA) of CIPRO XR?
The effects of food on the pharmacokinetics of ciprofloxacin following administration of a single dose of the 1000 mg XR formulation was investigated in a two-way crossover study. Subjects received study drug either after an overnight fast or a standard high-fat breakfast. As shown in the table below, ciprofloxacin pharmacokinetics are not altered by co- administration with food. The 90% CI for C_{max} and AUC demonstrated bioequivalence between fed and fasted conditions.

PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles

PK parameter*	1000 mg XR fasted (N=20)	1000 mg XR fed (N=20)
C_{max} (mg/mL)	2.83 (1.35)	3.12 (1.16)
AUC_{0-24} (mg-h/mL)	15.2 (1.35)	15.8 (1.19)
AUC_{inf} (mg-h/mL)	15.9 (1.36)	16.6 (1.21)
T_{max} (h)#	2 (0.5-3.5)	3.5 (2-4.0)
$T_{1/2}$ (h)	5.76 (1.13)	5.74 (1.12)

*Parameters are presented as geometric means (geometric SD)
#Values are medians for t_{max}

What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
CIPRO® XR can be administered without regard to meals.

How do the dissolution conditions and specifications assure in vivo performance and quality of the product?
Following are the proposed dissolution testing conditions and acceptance criteria

Apparatus:	USP Apparatus II (Paddle)
Dissolution medium:	900 mL 0.1N HCl
Bath temperature:	37 ± 0.5 °C
Rotation speed:	50 rpm
Acceptance Criteria:	30 minutes: (b) (4) %
	60 minutes: (b) (4) %
	120 minutes: NLT (b) (4) %

Based on the data provided by the applicant (see below), the proposed method and acceptance criteria are acceptable. The typical dissolution profile of ciprofloxacin 1000 mg tablets is given below:

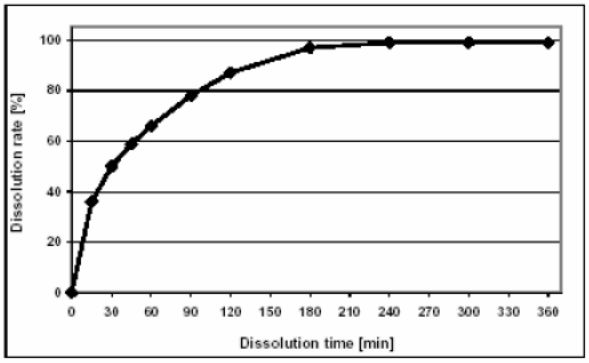


Fig. 1: Typical dissolution profile of Cipro MR Tablets 1 G
(USP paddle apparatus, 50 rpm, 0.1N HCl, 900 ml)

The influence of the pH of the dissolution medium upon the dissolution characteristics of ciprofloxacin 1000 mg tablets was studied. The dissolution data at each pH is given below:

Ciprofloxacin (b) (4) Tabl 1G Coat **765**, batch no 529234D (K-V/8), dissolution medium: **0.1N HCl**

sampling time	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	**Average [%]**	COV [%]
15 [min]	(b) (4)												**25**	27.2
30													**44**	12.0
45													**56**	7.6
60													**65**	6.2
90													**77**	5.9
120													**86**	5.4
180													**96**	3.5
240													**99**	2.5
300													**99**	2.6
360													**100**	2.6

Ciprofloxacin (b) (4) Tabl 1G Coat **765**, batch no 529234D (ME/S-X/2) diss: **0.01N HCl + NaCl**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**34**	14.0
30							**48**	5.3
45							**58**	5.2
60							**67**	5.8
90							**80**	5.8
120							**89**	4.4
180							**98**	1.8
240							**101**	2.2
300							**101**	2.2
360							**101**	2.3

Ciprofloxacin (b) (4) Tabl 1G Coat **765**, batch no 529234D (ME/S-IX/2), diss. medium: **acetate buffer pH 4.5**

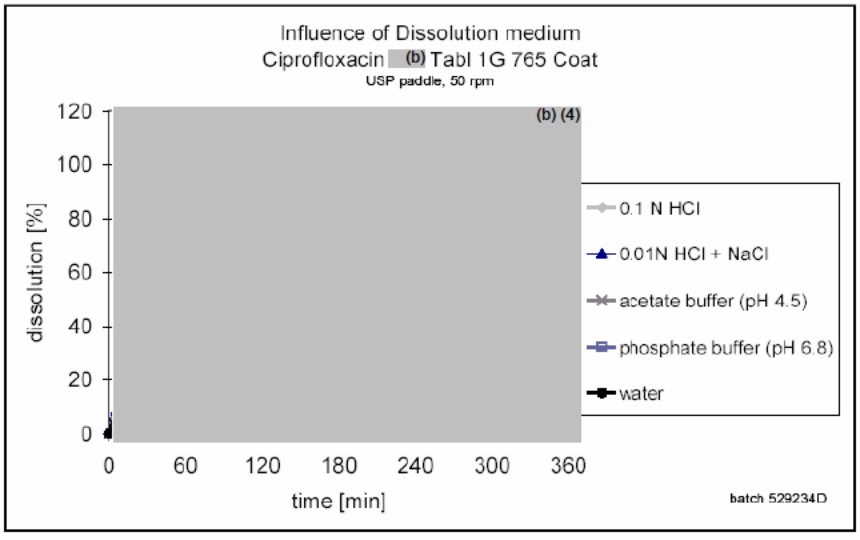
sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**27**	24.9
30							**44**	21.3
45							**56**	16.1
60							**65**	13.1
90							**78**	10.5
120							**88**	8.5
180							**98**	4.8
240							**101**	1.9
300							**101**	1.6
360							**101**	1.6

Ciprofloxacin (b) (4) Tabl 1G Coat **765**, batch no 529234D (ME/S-VIII/16), dissolution medium: **water**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**21**	19.5
30							**39**	19.1
45							**51**	15.2
60							**60**	11.5
90							**74**	7.9
120							**84**	5.2
180							**95**	2.8
240							**100**	1.3
300							**101**	1.0
360							**100**	1.2

Ciprofloxacin (b) Tabl 1G Coat **765**, batch no 529234D (ME/S-IX/6) diss. medium: **phosphate buffer pH 6.8**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**1**	11.7
30							**2**	6.2
45							**3**	4.5
60							**3**	3.8
90							**4**	3.1
120							**4**	3.0
180							**5**	3.1
240							**6**	3.3
300							**6**	3.8
360							**7**	3.9



The influence of the agitation rate upon the dissolution characteristics of ciprofloxacin 1000 mg tablets was studied.

Ciprofloxacin (b) (4) Tabl 1G Coat **760**, batch no 528480 E (K-V/1) diss. medium: 0.1N HCl, **50 rpm**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						32	18.7
30							50	4.1
45							61	2.0
60							69	2.3
90							80	2.5
120							88	1.9
180							97	1.4
240							100	2.1
300							100	2.1
360							100	2.2

Ciprofloxacin (b) (4) Tabl 1G Coat **760**, batch no 528480 E (ME/S-VIII/2) diss. medium: 0.1N HCl, **75 rpm**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						43	12.1
30							59	4.9
45							70	4.2
60							79	3.8
90							91	3.0
120							97	2.1
180							100	0.8
240							100	0.8

(b) (4)

How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The following assays were validated and used to determine ciprofloxacin concentrations in plasma and urine. A review of the analytical methodologies is presented below:

HPLC conditions of the assay in plasma samples:

Instrument: (b) (4)

(b) (4)

Internal Standard: Ofloxacin
Linearity: 0.01 – 2 mg/L
QC samples: 0.025, 0.25, 1.25 and 1.75 mg/L
Limit of Quantitation: 0.01 mg/L
Specificity and Accuracy: The (b) (4) procedures allowed a good separation of the components of interest from endogenous compounds.

A validation series (b) (4) yielded the following precision and accuracy data for ciprofloxacin:

Concentration [mg/L]	0.025	0.25	1.25	1.75
Accuracy (n=18) [%]	-4.36	-4.03	-2.49	-3.01
Precision (n=18) [%]	6.39	2.31	1.45	2.04

HPLC conditions of the assay in urine samples:

Instrument: (b) (4)

(b) (4)

Internal Standard: Ofloxacin
Linearity: 0.01 – 1 mg/L
QC samples: 0.50, 26.2 and 78.70 mg/L
Limit of Quantitation: 0.2 mg/L.
Specificity and Accuracy: The (b) (4) procedures allowed a good separation of the components of interest from endogenous compounds.

A validation series (b) (4) yielded the following precision and accuracy data for ciprofloxacin:

Concentration [mg/L]	0.50	26.20	78.70
Accuracy (n=6) [%]	-3.13	-3.19	-2.33
Precision (n=6) [%]	3.07	1.55	2.10

APPENDICES

1. Proposed labeling with Clinical Pharmacology Reviewer Comments
2. Clinical Pharmacology/Biopharmaceutics Individual Study Reviews
3. Review of the Monte-Carlo Simulation Report

24 page(s) has been Withheld in full as Draft labeling (CCI/TS) immediately following this page

Appendix-2: Clinical Pharmacology/Biopharmaceutics Individual Study Reviews

1. **Report 10324:** Open, Randomized, Non-Controlled, Multiple Dose, Twofold Cross-Over Study to Assess the Single Dose and Steady State Pharmacokinetics of the Oral Ciprofloxacin 1000mg Once Daily Tablet During a Five Days Treatment in Comparison to the BID Treatment with the 500mg Immediate Release Tablet in Healthy Male Subjects.

Objectives: Primary objective was to evaluate the single dose and steady state pharmacokinetics of an oral 1000 mg ciprofloxacin once daily tablet (CIPRO XR) given to healthy subjects after an overnight fast according to a once daily dosing regimen for five days. In addition a comparison to the standard immediate treatment regimen (500 mg immediate release given bid) was performed.

Investigator: (b) (4)

Formulations:

1. Ciprofloxacin Tablet Lack, 500 mg, batch number 5228631
2. Ciprofloxacin 1000 mg XR tablets, batch number 528480E

Subjects: 19 healthy subjects between 18 and 55 years were selected.

Study design: This was a single center, open label, randomized, non-controlled, multiple dose study in 19 healthy subjects and the treatment regimen was as follows:

- A: 1000 mg Ciprofloxacin once daily tablet formulation given once a day over a period of 5 days.
- B: 500 mg Ciprofloxacin standard tablet formulation (IR) tablet given bid over a period of 5 days.

The treatments were administered with a washout period of one week.

Sampling: For Treatment A, on day 0 and on day 4, 3 mL blood samples were collected in (b) (4) at 0, 0.5, 1.0, 2.0, 3, 3.5, 4, 6, 8, 12, 16 and 24 h following drug administration. For Treatment B, the sampling schedule was at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 6, 8, 12, 13, 13.5, 14, 15, 16 and 24 h following drug administration. The samples were centrifuged for 5 min at room temperature and (b) (4) g within 4 hours after collection. Plasma samples were stored at –20° C until analysis was performed.

The total and fractional volume of urine was collected on the profile days during the following intervals: 0-4, 4-8, 8-12 and 24-28 h. Aliquots of 9 mL each were provided from each interval from the spontaneous urine before first administration.

Assay: Ciprofloxacin was determined in all available plasma and urine samples using a (b) (4) method (b) (4). The internal standard used was Ofloxacin. The lower limit of quantitation was 0.01 mg/L in plasma samples and 0.2 mg/L in urine samples. The accuracy and precision of the assay

were 0.19-0.39% and 1.62-2.38%. The accuracy and precision of the urine assay were 3.99-4.51% and 2.11- 3.33%.

Pharmacokinetic Analysis: The pharmacokinetic analysis was performed by the noncompartmental method using (b) (4). The maximum plasma concentration (C_{max}), maximum plasma concentration ($C_{max\ ss}$) at steady state, time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{l/2}$), area under the plasma concentration versus time (AUC) curve, area under the plasma concentration versus time (AUC_{0-24}) curve for 0-24 hours, area under the plasma concentration versus time (AUC_{0-24ss}) curve for 0-24 hours at steady state, area under the plasma concentration curve versus infinite time (AUC_{inf}), amount excreted in urine (Ae_{ur})

Statistical Analysis: Exploratory statistical analyses by means of ANOVA were performed for the primary pharmacokinetic parameters of AUC, AUC_{0-24}, C_{max}, AUC_{0-24ss} and $C_{max\ ss}$ of ciprofloxacin in order to compare the pharmacokinetics of the once daily formulation and the standard tablet.

Results:
The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized in Table 1. Also presented are the 90% confidence intervals for the test/reference ratios.

Table 1. PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles

PK parameter*	Treatment A: XR tablet given once-daily	Treatment B: IR tablet given bid	Mean Ratio of XR tablet/IR tablet	90% CI
C_{max} (mg/mL)	2.53 (1.47)	1.94 (1.25)	1.34	1.20-1.49
AUC_{0-24} (mg-h/mL)	14.1 (1.50)	14.5 (1.30)	0.99	0.89-1.09
AUC_{inf} (mg-h/mL)	14.7 (1.52)	16.3 (1.34)	0.89	0.80-0.99
$AUC_{0-24\ ss}$ (mg-h/mL)	16.0 (1.38)	16.5 (1.31)	0.98	0.91-1.05
$C_{max\ ss}$	2.95 (1.40)	2.02 (1.22)	1.47	1.31-1.66
T_{max} (h)#	2.0 (1.0-3.5)	1.25 (0.5-3)	NC	NC
$T_{1/2}$ (h)	5.80 (1.12)	4.88 (1.17)	NC	NC
Ae_{ur} 0-24 (mg)	354 (99.9)	329 (74.8)	NC	NC

*Parameters are presented as geometric means (geometric SD) #Values are medians for tmax NC: Not Calculated

Figure 11.5.2-1: Plasma concentration vs time curves for ciprofloxacin (BAY q 3939) including the geometric standard deviation in study 10324 (N=18)

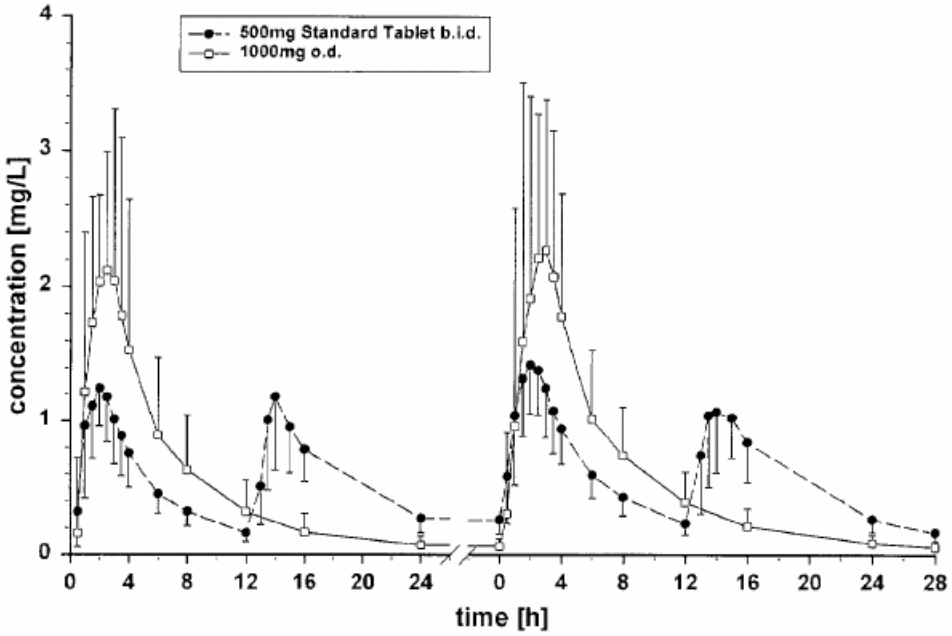
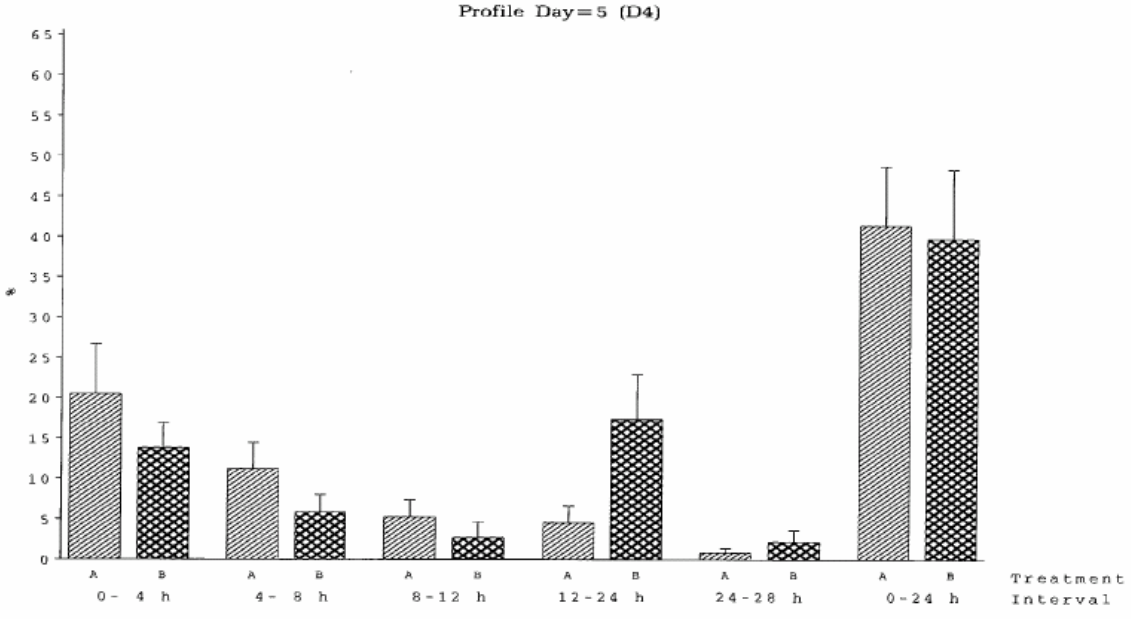


Figure 14.4−1.2
Mean Bar Chart for BAY Q 3939 Amount Excreted Into Urine (%)
All subjects valid for PK and safety (N=18)



Treatment Key: A − 1000 mg BAY q 3939 od, B − 500 mg BAY q 3939 bid

The AUC_{inf} of the 1000 mg ciprofloxacin once daily formulation was slightly lower (11%) than the bid treatment with the IR tablet. However, the 90% confidence intervals were within the 80-125% bioequivalence range.

The C_{max} of the 1000 mg ciprofloxacin once daily formulation was 34% higher than after the 500 mg bid treatment with the IR tablet. Also $C_{max\ ss}$ was increased by 47% comparing the 1000 mg XR tablet with the 500 mg bid tablet. This higher C_{max} following administration of the XR formulation may be due to the immediate release (IR) component in the XR formulation.

As seen in the above table, AUC and C_{max} were essentially not different between steady state and single dose suggesting linear pharmacokinetics and absence of significant accumulation.

As seen in Table 1 and in the Figure 2, the amount of ciprofloxacin excreted unchanged in urine (Ae_{ur}) was comparable for the XR formulation and the IR formulation. In the urine, higher ciprofloxacin concentrations were reached for the XR formulation in the period until 12 hours post dosing compared to the IR tablet.

Summary and Conclusions:
The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new XR formulation to healthy male subjects resulted in comparable extent of exposure pharmacokinetic parameters (AUC, Ae_{ur}) suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation. Peak exposure (C_{max}) was approximately 30-40% higher with the XR formulation than with the immediate-release formulation.

2. **Study 10339**: **Not blind, randomized, triple cross-over, non-controlled study to compare the safety, tolerability and pharmacokinetics of two oral ciprofloxacin 1000 mg once daily tablet formulations administered as a single dose in the fed state and two doses of the 500 mg standard tablet given 12 h apart after an overnight fast to healthy male subjects.**

Objectives: Primary objective was to compare the safety, tolerability and pharmacokinetics of two oral 1000 mg ciprofloxacin once daily formulations given after a continental breakfast with the marketed ciprofloxacin product given orally according to a bid dosing schedule as two doses of 500 mg to healthy subjects who fasted overnight.

Investigator: (b) (4)

Formulations:

- Ciprofloxacin Tablet (b) (4), 500 mg, batch number 522863L
- Ciprofloxacin 1000 mg XR tablets, batch number 528480E (Formulation E760)
- Ciprofloxacin 1000 mg XR tablets, batch number 528613A (Formulation E780)

Subjects: 12 healthy subjects between 18 and 55 years were selected.

Study design: This was a single center, open-label, randomized, non-controlled study in 12 healthy male subjects and the treatment regimen was a single dose treatment with two 1000 mg Ciprofloxacin once daily tablet formulation (XR) given 15 minutes at the end of a continental breakfast (4 slices toast, 20g butter, 50g jam, 20g cheese, 200mL decaffeinated coffee, 3g sugar) and bid treatment with two 500 mg doses of the marketed standard tablet (IR, first dose given after an overnight fast).

The treatments were administered with a washout period of one week.

Sampling: For 1000 mg single dose administration, 3 mL blood samples were collected in (b) (4) at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 16 and 24 h following drug administration. For 500 mg bid treatment with standard tablet, the sampling schedule was at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 13, 13.5, 14, 14.5, 15, 15.5, 16, 20, 24 and 30 h following drug administration. The samples were centrifuged for 5 min at room temperature and (b) (4) g within 4 hours after collection. Plasma samples were stored at –20° C until analysis was performed.

Assay: Ciprofloxacin was determined in all available plasma samples using a (b) (4) method with (b) (4) The internal standard used was Ofloxacin. The lower limit of quantitation was 0.01 mg/mL in plasma and 0.2 mg/mL in urine. The accuracy and precision of the plasma assay were 0.26-1.61% and 0.98-1.71 %. The accuracy and precision of the urine assay were 3.34-9.72% and 1.58-4.96 %.

Pharmacokinetic Analysis: The pharmacokinetic analysis was performed by the noncompartmental method using (b) (4) The maximum

plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{l/2}$), area under the plasma concentration versus time (AUC) curve, area under the plasma concentration versus time (AUC_{0-24}) curve for 0-24 hours and area under the plasma concentration curve versus infinite time (AUC_{inf}).

Statistical Analysis: Exploratory statistical analyses by means of ANOVA were performed for the primary pharmacokinetic parameters of AUC, AUC_{0-24} and C_{max} of ciprofloxacin in order to compare the pharmacokinetics of the once daily formulation and the standard tablet.

Results:
The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized in Table 3. Also presented are the 90% confidence intervals for the test/reference ratios.

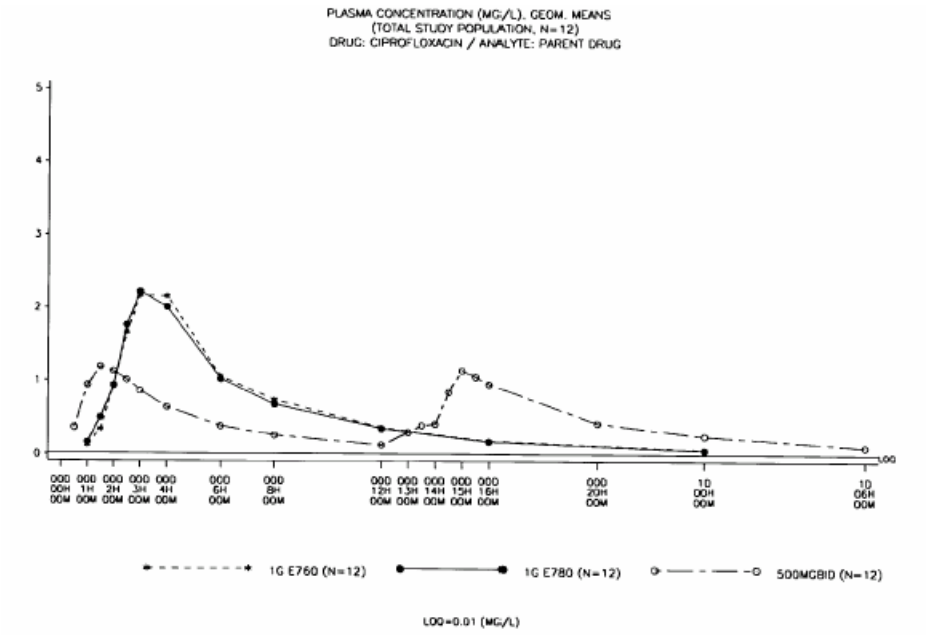
Table 2. PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles

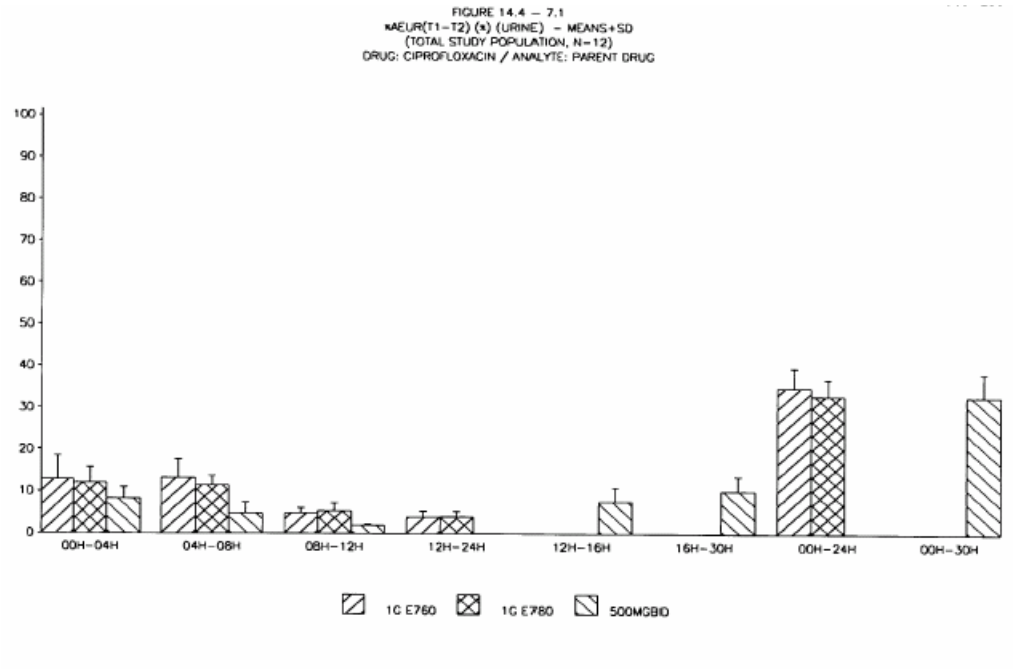
PK parameter*	500 mg bid fasted	1000 mg XR (E760) fed (N=12)	1000 mg XR (E780) fed (N=12)
C_{max} (mg/mL)	1.56 (1.38)	2.95 (1.30)	2.56 (1.24)
AUC_{0-24} (mg-h/mL)	13.4 (1.37)	14.2 (1.22)	13.5 (1.28)
AUC_{inf} (mg-h/mL)	15.4 (1.34)	14.8 (1.23)	14.0 (1.29)
T_{max} (h)[#]	1.75 (0.5-2.53)	3.0 (1.5-4.0)	3.0 (1.5-4.0)
$T_{1/2}$ (h)	5.20 (1.18)	5.21 (1.14)	4.94 (1.09)

*Parameters are presented as geometric means (geometric SD)
#Values are medians for t_{max}

Table 11.5.4-1: Point estimators (LS-means) and (exploratory) two-sided 90% confidence intervals for the ratios '1000 mg OD (E760) fed / 500 mg bid fasted' and '1000 mg OD (E780) fed / 500 mg bid fasted' with regard to the primary pharmacokinetic parameters AUC, AUC_{0-24} and C_{max} of ciprofloxacin (all subjects valid for PK, N=12)

Ratio	Parameter	N	estimated ratio (%)	90% confidence interval
1000 mg OD (E760) fed/	AUC	12	95.55	[87.95 ; 103.79]
500 mg bid fasted	AUC_{0-24}	12	105.95	[96.76 ; 116.02]
	C_{max}	12	189.31	[169.19 ; 211.83]
1000 mg OD (E780) fed/	AUC	12	90.59	[83.39 ; 98.41]
500 mg bid fasted	AUC_{0-24}	12	100.89	[92.13 ; 110.48]
	C_{max}	12	164.14	[146.69 ; 183.66]





As shown in Table 3, the point estimators suggest that the oral bioavailability (AUC_{inf}) of ciprofloxacin was 96% and 91% after the 1000 mg XR formulations E760 and E780 when compared to the 500 mg bid reference treatment. The 90% confidence intervals met the bioequivalence acceptance range of 80-125%.

As seen in the above Figure (14.4-7.1), the amount of ciprofloxacin excreted unchanged in urine (Ae_{ur}) was comparable for the XR and IR formulations.

Summary and Conclusions:
After single dose administration of 1000 mg ciprofloxacin as XR tablet formulations E760 and E780 under fed conditions compared to the 500 mg IR standard tablet bid under fasted condition the relative bioavailability of ciprofloxacin was 96% and 91%, respectively.

3. **Report 10321: Not-blind, randomized, single dose, two-fold crossover, non-controlled study to evaluate the effect of a high calorie, high fat meal on the pharmacokinetics of a ciprofloxacin 1000 mg XR formulation in healthy male subjects.**

Objectives: The primary objective of the study was to evaluate the effect of a high calorie, high fat meal on the pharmacokinetics of a new oral Ciprofloxacin 1000 mg XR formulation given to healthy subjects who fasted overnight.

Investigator: (b) (4)

Formulations:
Ciprofloxacin Tablet, 500 mg, batch number 528481C

Subjects: 20 healthy subjects between 18 and 55 years were selected.

Study design: This was a single center, open-label, randomized, non-blinded, two-way crossover non-controlled study in 20 healthy male subjects; single dose treatment with the 500 mg Cipro XR formulation given on two occasions:

- Administered after an overnight fast with 180 mL non-sparkling water.
- Administered 5 minutes after the end of a high calorie, high fat meal, eaten within 30minutes after a 10 hour fast, with 180 mL of non-sparkling water.

The treatments were separated by a washout period of at least one week.

Sampling: 3 mL blood samples were collected in (b) (4) at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 6, 8, 12, 15 and 24 h following drug administration. The samples were centrifuged for 5 min at room temperature and (b) (4) g within 4 hours after collection. Plasma samples were stored at –20° C until analysis was performed.

Assay: Ciprofloxacin was determined in all available plasma samples using (b) (4) method (b) (4). The internal standard used was Ofloxacin. The lower limit of quantitation in plasma and urine were 0.01 and 0.2 mg/mL, respectively. The accuracy and precision of the plasma assay were 0.86 - 0.65% and 2.32 - 4.11 %. The accuracy and precision of the urine assay were 2.68 - 5.06% and 1.65 - 4.40 %.

Pharmacokinetic Analysis: The pharmacokinetic analysis was performed by the noncompartmental method using the (b) (4) The maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{l/2}$), area under the plasma concentration versus time (AUC) curve, area under the plasma concentration versus time (AUC_{0-24}) curve for 0-24 hours and area under the plasma concentration curve versus infinite time (AUC_{inf}).

Statistical Analysis: Exploratory statistical analyses by means of ANOVA were performed for the primary pharmacokinetic parameters of AUC, AUC_{0-24} and C_{max} of

ciprofloxacin in order to compare the pharmacokinetics of the once daily formulation and the standard tablet.

Results:
The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized in Table 6. Also presented are the 90% confidence intervals for the test/reference ratios.

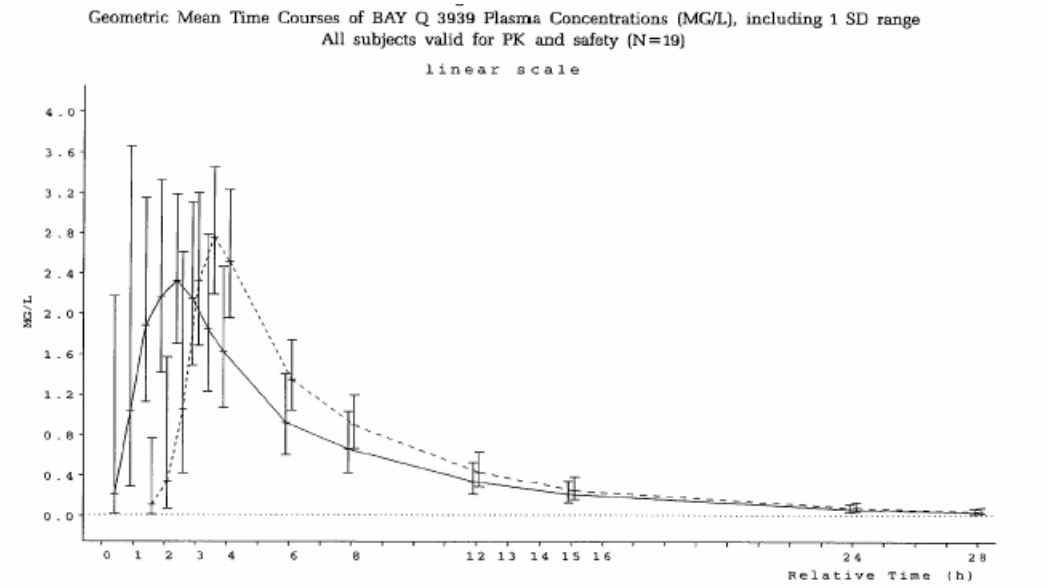
Table 3. PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles

PK parameter*	1000 mg XR fasted (N=20)	1000 mg XR fed (N=20)
C_{max} (mg/mL)	2.83 (1.35)	3.12 (1.16)
AUC_{0-24} (mg-h/mL)	15.2 (1.35)	15.8 (1.19)
AUC_{inf} (mg-h/mL)	15.9 (1.36)	16.6 (1.21)
T_{max} (h)#	2 (0.5-3.5)	3.5 (2-4.0)
$T_{1/2}$ (h)	5.76 (1.13)	5.74 (1.12)

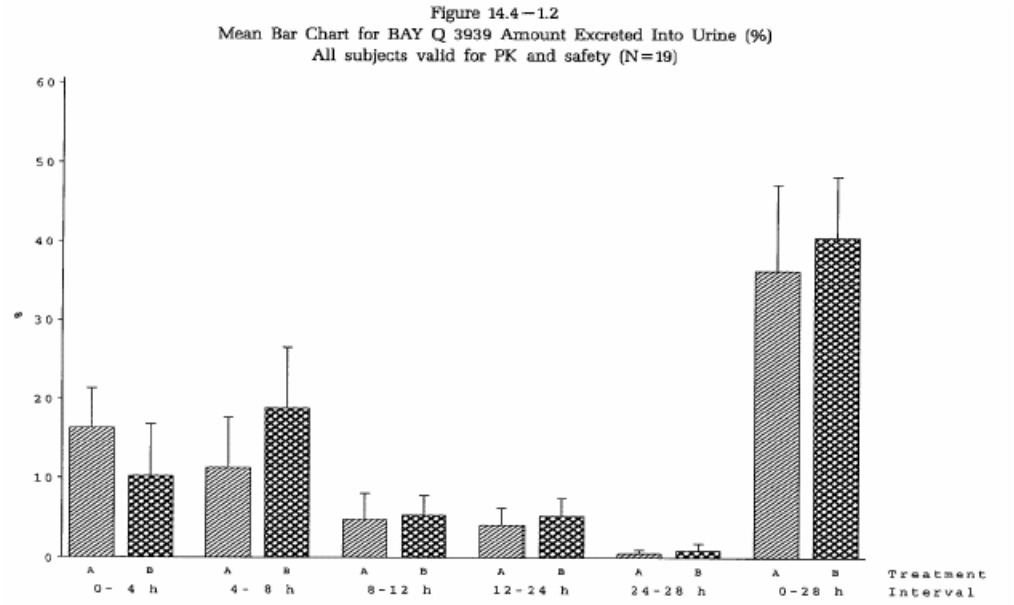
*Parameters are presented as geometric means (geometric SD)
#Values are medians for t_{max}

Table 11.5.4-1: Mean ratios and 90% confidence intervals for primary parameters C_{max}, AUC, and AUC_{0-24} of ciprofloxacin

Parameter	Mean ratio Fed/Fasted	90% confidence interval	Within-Subject CV (%)
C_{max}	1.098	(0.996, 1.210)	17.32
AUC	1.042	(0.945, 1.148)	17.36
AUC_{0-24}	1.035	(0.939, 1.142)	17.44



Note: Solid line = 1000 mg BAY q 3939 in fasted state, dashed line = 1000 mg BAY q 3939 in fed state
Values below LOQ (0.01 mg/l) were replaced by half of LOQ in calculations if at least 2/3 of the data were above LOQ.



Treatment Key: A – 1000 mg BAY q 3939 in fasted state, B – 1000 mg BAY q 3939 in fed state

As shown in Table 6, the 90% CI for the mean ratios were completely within the required bioequivalence ranges for AUC, AUC_{0-24} and C_{max}, respectively. Thus, the 500 mg XR ciprofloxacin in the fasting and fed states are bioequivalent. The T_{max} was prolonged from 2 hr to 3.5 hours following administration of the XR tablet with food.

As seen in the above Figure (14.4-1.2), the amount of ciprofloxacin excreted unchanged in urine (Ae_{ur}) was comparable for the XR formulations under fed and fasted conditions.

Summary and Conclusions:
Based on the above results, it may be concluded that with respect to AUC_{0-24}, AUC_{inf} and C_{max}, a clinically relevant food effect is absent.

Appendix-3: Review of the Monte-Carlo Simulation Report

Report No.: PH-32741: A new [redacted] (b) (4) Ciprofloxacin XR® tablet: Pharmacokinetic simulations of different dosing regimens in renally impaired patients compared to the standard Cipro® IR tablet

Objectives:
To establish a pharmacokinetic model of ciprofloxacin from Phase studies in healthy volunteers after oral administration of Cipro IR and Ciprofloxacin XR for 5 days bid and qd, respectively.

To compare the effect of renal impairment on the single dose and steady state pharmacokinetics of ciprofloxacin, when given orally in form of an immediate release standard tablet (Cipro®) and as a [redacted] (b) (4) tablet (Ciprofloxacin XR®) to healthy subjects by means of population pharmacokinetic simulations based on available Phase I studies.

The following Monte-Carlo simulations have been performed to estimate the influence of renal function on the plasma pharmacokinetics under different dosing regimens:

1. Pharmacokinetics of ciprofloxacin in patients with severe renal impairment (CLcr < 30 mL/min/1.73m²) receiving 500 mg Ciprofloxacin XR® tablets once daily for three days
2. Pharmacokinetics of ciprofloxacin in patients with mild to moderate renal impairment (90 mL/min/1.73m² > CLcr > 30 mL/min/1.73m²) receiving 500 mg Cipro® tablets twice daily for three days
3. Pharmacokinetics of ciprofloxacin in patients with severe renal impairment (CLcr < 30 mL/min/1.73m²) receiving 500 mg Cipro® tablets once daily or once every 18 hours for three days
4. Pharmacokinetics of ciprofloxacin in subjects with normal renal function receiving 750 mg Cipro® tablets twice daily for 14 days Monte Carlo simulations have been done by using nonlinear mixed

Methodology:
Monte Carlo simulations have been done by using nonlinear mixed effect modeling established within NONMEM V version 1.1. The model for the PK of ciprofloxacin as XR and IR tablet has been established with data from Phase I trials in healthy male volunteers (Study #PPK 02-006). The exposure parameters Cmax and AUC were estimated by using SAS 8.2 and WinNonlin 4.0.1 (Pharsight Inc.). For each simulation scenario the plasma-concentration time profile of a typical subject has been simulated 100 times. From these profiles descriptive statistics were calculated.

Assumptions:
Since no experimental data are available in renally impaired patients for the Ciprofloxacin XR, the following assumptions were made:

1. The pharmacokinetic parameters V_c, V_p, Q, Ka and lag time as well as their estimates of variability are assumed to be not affected by renal impairment. In addition, it was also assumed that the variability of CL/f of ciprofloxacin is not altered by renal impairment. Previous pharmacokinetic evaluation in renally impaired patients exhibited somewhat lower volume of distribution expressed as V_{ss} in severe renal impairment. However, other study data indicate that the volume of distribution expressed as V_z/f was not influenced by CL_{cr}. Consequently, the volume parameters estimated in the Phase I studies in healthy volunteers were assumed to be independent of renal function, which would be consistent with general pharmacokinetic knowledge. This assumption is supported by the results of the model validation in renally impaired subjects.
2. To describe the influence of renal impairment on the plasma pharmacokinetics of ciprofloxacin after oral administration of Ciprofloxacin XR., the linear relationship established previously after intravenous administration of ciprofloxacin to renally impaired patients between total body clearance and creatinine clearance can be transferred as follows into the model:
   Ciprofloxacin XR®: CL/f (L/h) = 67.4 + 0.4156 * (CL_{cr} –120) (mL/min/1.73 m²) - 67.4 L/h - 0.4156 (slope of CL=f (CL_{cr}) after intravenous administration = 0.2909 slope corrected for bioavailability (F) in CL/f of ciprofloxacin (70 %)) - 120 mL/min/1.73 m²: Average CL_{cr} of healthy male Cipro® IR: CL/f (L/h) = 65.6 + 0.4156 * (CL_{cr} –120) (mL/min/1.73 m²) - 65.6 L/h – Estimate of CL/f (PK model 190 – PK of Cipro® IR, see Appendix)
3. Other covariates found during prior modeling (like weight influencing CL) were held constant, i.e. values assigned in a way that these covariates do not influence the simulation (Standard patient: body height = 180 cm, body weight = 80 kg, FAT=18 (they are set to the mean values in the data underlying the model)).
4. The bioavailability of ciprofloxacin is known to be not influenced by renal impairment. Therefore, f was setup independent of renal function as 70 % as determined in various studies.
5. The studies (IMPACT # 10324 and 10325) used for model development were performed in healthy male volunteers. Since no relevant gender influence on the pharmacokinetics of ciprofloxacin is currently known, the simulation using the population PK model from healthy male volunteers incorporating the linear relationship of CL with CL_{cr} from male and female patients is considered to be relevant for male and female subjects.

All evaluations as far as modeling and simulation were performed using NONMEM V level 1.1, S-Plus 3.1 and SAS 8.2 (b) (4) The pharmacokinetic parameter $AUC_{(0-24)}$ was calculated using WinNonlin 4.0.1 (Pharsight Inc.) according to the lin/log trapezoidal rule. The exposure parameter C_{max} as well as the statistical evaluations such as geometric mean and geometric standard deviation was calculated within SAS.

Results:
Simulation results

In the present study the influence of renal impairment on the pharmacokinetics of ciprofloxacin following oral administration of the standard tablet and the new Ciprofloxacin XR® tablet formulation was evaluated by means of Monte Carlo simulations. The structural population pharmacokinetic model including subjects' covariates only for body weight (covariate for CL) and FAT (covariate for peripheral volume) was developed by nonlinear mixed effect modeling implemented in NONMEM. The influence of renal impairment, which decreases the renal clearance of ciprofloxacin as one major clearance pathway, was factored in by implementing the linear functional relationship between kidney function (i.e. creatinine clearance) and renal clearance derived from studies in patients with various degrees of renal impairment following intravenous administration [9]. Based on the resulting structural model plasma concentration vs. time profiles were simulated for 100 patients with both covariates (body weight and fat content) of a typical subject for the following four simulation scenarios :

Simulation Scenario	Dosing regimen	Simulation Results
1	500 mg Ciprofloxacin XR® qd for 3 days in patients with severe renal impairment	Table 10-8 Figure 10-8 Figure 10-9
2	500 mg Cipro® IR bid for 3 days in patients with mild to moderate renal impairment	Table 10-9 Figure 10-10 Figure 10-11
3a	500 mg Cipro® IR qd for 3 days in patients with severe renal impairment	Table 10-10 Figure 10-12 Figure 10-13
3b	500 mg Cipro® IR every 18 hours for 3 days in patients with severe renal impairment	Table 10-11 Figure 10-14 Figure 10-15
4	750 mg Cipro® IR bid for 14 days in patients with normal renal function	Table 10-12 Figure 10-16

For each scenario, peak concentrations and exposure (C_{max}, AUC, $AUC_{(0-24)}$) were evaluated by descriptive univariate statistical methods. The results are summarized in Table 10-8 to Table 10-12 and Figure 10-8 to Figure 10-16 (including plots of individual profiles (“spaghetti plots”)).

Exposure Comparison of the different Simulation Scenarios

Table 10-1: Comparison of predicted Cmax [mg/L] for the different simulation scenarios [geo. mean/geom. sd (range)]

Scenario	Dosing regimen	Simulation Results
1	500 mg Ciprofloxacin XR® qd for 3 days in patients with severe renal impairment	Day 1: 2.14/1.51 (0.58-5.74) Day 3: 2.49/1.43 (0.82-6.13)
2	500 mg Cipro® IR bid for 3 days in patients with mild to moderate renal impairment	Day 1: 2.55/1.56 (0.85-7.03) Day 3: 2.98/1.49 (1.02-7.03)
3a	500 mg Cipro® IR qd for 3 days in patients with severe renal impairment	Day 1: 2.49/1.61 (0.59-7.11) Day 3: 2.92/1.53 (1.13-8.01)
3b	500 mg Cipro® IR every 18 hours for 3 days in patients with severe renal impairment	Day 1: 2.99/1.58 (1.23-9.55) Day 3: 3.12/1.51 (1.32-9.5)
4	750 mg Cipro® IR bid for 14 days in patients with normal renal function	Day 1: 3.22/1.6 (0.64-9.27) Day 14: 3.63/1.58 (1.09-9.42)

Figure 10-1: Comparison of predicted C_{max} [mg/L] for simulation scenario 1-4 Bloxplots: Boxes show the median, 25 % and 75 % percentiles. Whiskers extend from the box to the most extreme value within 1.5 interquartile range. More extreme values are displayed with dots

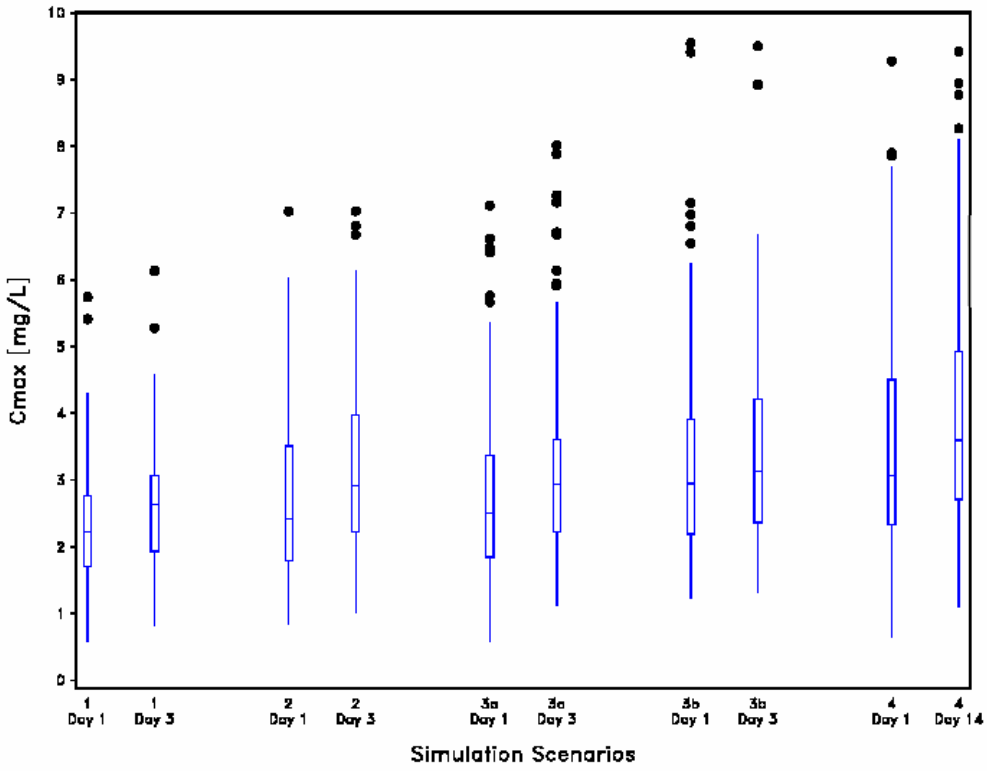
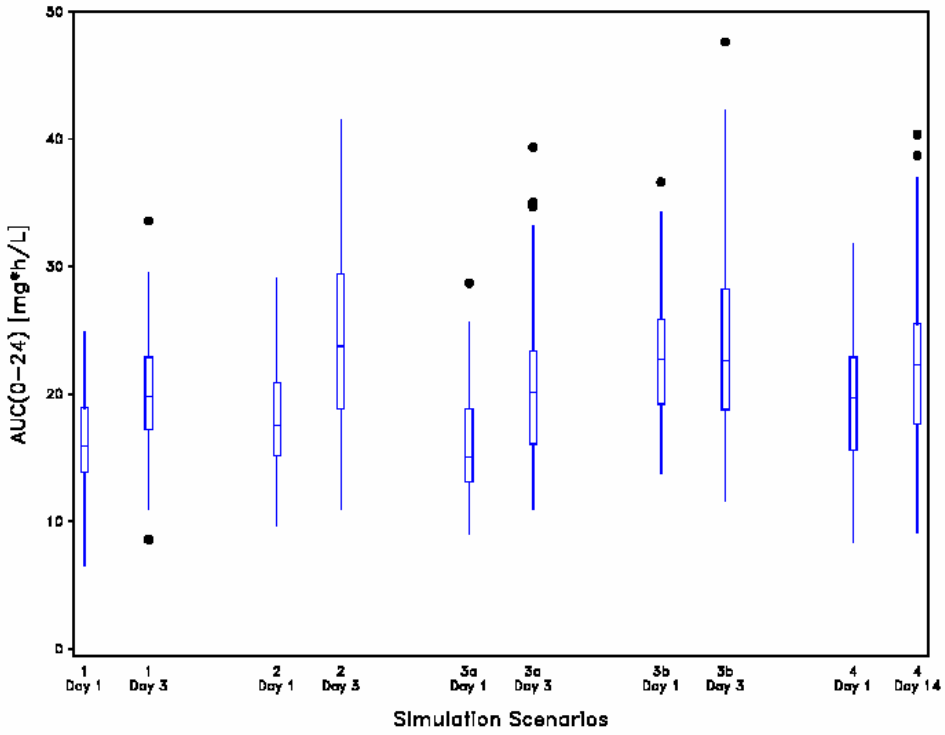


Table 10-2: Comparison of predicted AUC(0-24) [mg*h/L] [geo. mean/geom. sd (range)]

Scenario	Dosing regimen	Simulation Results
1	500 mg CiproXR® qd for 3 days in patients with severe renal impairment	Day 1: 15.74/1.27 (6.51-24.86) Day 3: 19.49/1.27 (8.59-33.58)
2	500 mg Cipro® IR bid for 3 days in patients with mild to moderate renal impairment	Day 1: 17.47/1.27 (9.64-29.12) Day 3: 23.04/1.36 (10.92-41.52)
3a	500 mg Cipro® IR qd for 3 days in patients with severe renal impairment	Day 1: 15.47/1.29 (9-28.7) Day 3: 19.78/1.34 (10.97-39.36)
3b	500 mg Cipro® IR every 18 hours for 3 days in patients with severe renal impairment	Day 1: 22.15/1.26 (13.79-36.63) Day 3: 23.25/1.37 (11.61-47.63)
4	750 mg Cipro® IR bid for 14 days in patients with normal renal function	Day 1: 18.84/1.31 (8.33-31.78) Day 14: 21.6/1.34 (9.12-40.36)

Figure 10-2: Comparison of predicted AUC(0-24) [mg*h/L] for simulation scenario 1-4
Bloxplots: Boxes show the median, 25 % and 75 % percentiles. Whiskers extend from the box to the most extreme value within 1.5 interquartile range. More extreme values are displayed with dots.



The simulations predict that the highest drug concentrations are reached in subjects with healthy kidney function receiving a 750 mg bid IR dosing schedule (Scenario 4) or patients with severe renal impairment receiving a 500 mg IR dose every 18 hours (Scenario 3b). For scenario 1, variability of the C_{max} predictions was the lowest among all dosing regimen simulated. With respect to extent and variability of drug exposure scenario 1 (XR tablet, qd, severe renal impairment) and 3a (IR tablet, qd, severe renal impairment) were comparable as expected from the clinical pharmacokinetic properties of both formulations. Highest exposure data (extent and variability) were predicted for the scenario 3b (500 mg every 18 hours, severe renal impairment) with the extremes exceeding the predictions for the highest approved dosing regimen (750 mg bid, scenario 4), which is in accord with the pharmacokinetic properties of ciprofloxacin.
The exposure data confirm the conclusions drawn from clinical study data for dose adjustments in patients with severe renal impairment.

Overall Summary and Conclusion
The simulations predict that the maximum approved dosing regimen of 750 mg bid for the treatment of severe infections in patients with normal kidney function covers peak concentrations and exposure resulting from application of 500 mg ciprofloxacin qd in form of the XR® tablet in patients with severe renal impairment.

Reviewer Comments:
1. It appears the applicant used First-Order (FO) method in the modeling and simulation. It is known that First Order Conditional Estimation (FOCE/INTERACTION) method is preferable for a relatively dense data set. Please address why only FO was used.

2. In the simulation, according to the code, CL_{cr} of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renal impaired and severe renal impaired, respectively. The approach is considered to be inadequate. It is preferable to simulate with continuous distribution of CL_{cr} ranges of normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment.

3. The applicant used the established relationship (published data) between clearance (CL) of ciprofloxacin and creatinine clearance (CL_{cr}). However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of oral Cipro IR formulation and use it for the purpose of modeling and simulations. We recommend that the applicant re-develop the relationship between clearance (CL) and creatinine clearance (CL_{cr}) and compare with the previous results.

4. Based on review of the Monte-Carlo simulations, the safety of CIPRO XR 500 mg administered QD to patients with uncomplicated UTI and severe renal impairment is acceptable. Also, based on principles of linear pharmacokinetics, extrapolation of the exposure can be made from the 3-day regimen in uncomplicated UTI to 14-day

regimen in complicated UTI and acute pyelonephritis. This means that the applicant's proposal to reduce the dosage from CIPRO XR 1000 mg to 500 mg for patients with complicated UTI and severe renal impairment is acceptable from a safety perspective.

5. The issue of dosage adjustment of CIPRO XR 1000 mg to patients with complicated UTI and acute pyelonephritis and mild to moderate renal impairment has not been addressed by the applicant in NDA 21-554. Specifically, it is unknown if the C_{max} and AUC following administration of CIPRO XR 1000 mg to patients with mild to moderate renal impairment would result in exposure causing higher incidence of adverse events. It is recommended that the applicant perform Monte-Carlo simulations to obtain exposure information following administration of CIPRO XR 1000 mg in patients with mild to moderate renal impairment.

6. Upon review of the safety data in Clinical Study 100275, the adverse events observed following administration of CIPRO XR 1000 mg to patients with normal renal function and to patients with mild to moderate renal impairment are similar. However, the exposure following administration of CIPRO XR 1000 mg to patients with mild to moderate renal impairment is likely to be higher than the exposure obtained after administration of 750 mg bid. But considering the overall safety profile of ciprofloxacin, it may be acceptable to administer a dose of CIPRO XR 1000 mg to patients with mild to moderate renal impairment suffering from complicated UTI. As a Phase IV commitment, the applicant should be asked to perform Monte-Carlo simulations to obtain the exposure of ciprofloxacin in mild to moderate renally impaired patients. Based on the information obtained from the simulations, changes in labeling recommendations may be made.

Recommendations:

1. It appears the applicant used FO method in the modeling and simulation. It is known that FOCE/INTERACTION method is preferable for a relatively dense data set. Please address why only FO was used.

2. In the simulation, according to the code, CL_{cr} of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renally impaired and severely renal impaired, respectively. This approach is considered to be inadequate. It is preferable to simulate with ranges of CL_{cr} values for normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment. Therefore, as a Phase IV commitment, please perform additional Monte-Carlo simulations to obtain estimates of ciprofloxacin systemic exposure after administration of the following regimens:

- 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
- 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4) 50 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)

- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4)-50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CL_{cr} (b) (4) 120 mL/min)

Based on the information obtained from the above-mentioned simulations, adjustments to the dosage regimen for CIPRO® XR 1000 mg in patients with mild and/or moderate renal impairment may be needed.

3. The applicant used the established relationship between clearance (CL) of intravenously administered ciprofloxacin and creatinine clearance (CL_{cr}). However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of the orally administered Cipro IR tablet and use it for the purpose of modeling and simulations. We recommend that the applicant re-develop the relationship between oral ciprofloxacin clearance and creatinine clearance (CL_{cr}) and compare with the previous results.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dakshina Chilukuri
8/14/03 09:51:22 AM
BIOPHARMACEUTICS

Phil Colangelo
9/15/03 03:49:47 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-554

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Section 14 – Patent Certification

All investigations relied upon by Bayer Corporation in this NDA were conducted by or for Bayer using drug substance and drug product in accordance with the patents listed in the Patent Information Section.

Please refer to Section 13, Patent Information.

Section 13: The following information is hereby provided pursuant to 21 C.F.R. § 314.53(c):

Patent Number:	4,670,444
Expiration Date:	December 9, 2003
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

The undersigned declares that the U.S. Patent Number 4,670,444 covers the formulation, composition and method of use of ciprofloxacin. This product is the subject of this application for which approval is being sought.

Mary E. Taylor, MPH
Vice President, Regulatory Affairs
Bayer Corporation

EXCLUSIVITY SUMMARY for NDA # 21-554 SUPPL #
Trade Name CIPRO® XR Generic Name ciprofloxacin extended release tablets
Applicant Name Bayer Pharmaceuticals Corporation HFD- 590

Approval Date August 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/____/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/NO /_X_ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-537 Cipro® tablets

NDA # 20-780 Cipro® oral suspension

NDA # 19-847, 19-857, 19-858 Cipro® I.V.

NDA # 21-473 Cipro® XR

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/NO/___/N/A_X_

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 100275

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # 100275

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 61,331 YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Jouhayna S. Saliba, Pharm.D.
Signature of Preparer
Title: Regulatory Health Project Manager

Renata Albrecht, M.D.
Signature of Division Director

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Jouhayna Saliba
12/17/03 10:57:37 AM

Renata Albrecht
12/17/03 04:42:31 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-554 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: October 29, 2002 **Action Date:** August 28, 2003

HFD-590 **Trade and generic names/dosage form:** CIPRO® XR (ciprofloxacin extended release tablets)

Applicant: Bayer Pharmaceuticals Corporation **Therapeutic Class:** quinolone

Indication(s) previously approved: Uncomplicated urinary tract infection

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Complicated urinary tract infection

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: 0-16 years

Min _____ kg_____ mo._____ yr._0____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__16___ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- **X There are safety concerns**
- **X Adult studies ready for approval**
- **X Formulation needed**

Other:_____

Date studies are due (mm/dd/yy):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jouhayna S. Saliba, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Acute Uncomplicated pyelonephritis

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:0-16 years

Min _____ kg_____ mo._____ yr.__0___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__16__ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- **X There are safety concerns**
- **X Adult studies ready for approval**
- **X Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Jouhayna S. Saliba, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jouhayna Saliba

10/17/03 02:31:54 PM

Section 16 : Debarment Certification

Bayer hereby certifies under FD&C Act, Section 306 (k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Mary E. Taylor, MPH
Vice President, North America Regulatory Affairs
Bayer Corporation

DESK COPY

Bayer HealthCare
Pharmaceuticals

August 28, 2003

Renata Albrecht, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-554
CIPRO® XR (ciprofloxacin extended-release tablets) 1000 mg
Response to FDA Request for Information
Phase IV Commitments

Bayer Pharmaceuticals
Corporation
400 Morgan Lane
West Haven, CT 06516

Tel. 203 812-2000
www.bayer.com

Dear Dr. Albrecht,

Reference is made to the Cipro XR NDA, 21-554, currently under review by the Division. As proposed in recent discussions and correspondence between Bayer and the Division, Bayer Pharmaceuticals Corporation agrees to the following Phase IV commitments as a condition of approval for this NDA:

1. Provide confirmative evidence of CIPRO XR efficacy in treating complicated urinary tract infections caused by *P. aeruginosa*.

- Protocol submission by no later than six months from date of approval.
- Study start by no later than twelve months from the date of approval.
- Final report submitted by no later than thirty-nine months from the date of approval.

2. Perform Monte Carlo simulations to obtain steady state estimates of ciprofloxacin systemic exposure after administration of the following regimens. These simulations are to be performed over the ranges of creatinine clearance (CLcr) values specified below for normal renal function and mild, moderate, and severe renal impairment, rather than using a single CLcr value:

- 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CLcr 50-80mL/min)
- 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CLcr 30-50 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CLcr <30 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CLcr 50-80 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CLcr 30-50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CLcr 81-120 mL/min)

Final Report Submission: Within 12 months from the date of approval

If any questions or concerns arise from this information, do not hesitate to contact me at (203) 812-5172 or at andrew.verderame.b@bayer.com.

Sincerely,

Andrew S. Verderame
Director, Regulatory Affairs

Desk copy : Jouhayna Saliba, PharmD, Project Manager

8/28/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-554	Efficacy Supplement Type SE-	Supplement Number	
Drug: **CIPRO® XR**		Applicant: **Bayer Pharmaceutical Corporation**	
RPM: **Jouhayna Saliba, Pharm.D.**		**HFD-590**	Phone # 301-827-2127
Application Type: **(X)** 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**August 29, 2003**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	**(X)** Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ Patent	
• Information: Verify that patent information was submitted	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	**X**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**X**
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**N/A**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(X)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
• Most recent applicant-proposed labeling	**X**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**X**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**X**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**X**
• Reviews	**See CMC review**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**X**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**X**
❖ Memoranda and Telecons	**N/A**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**N/A**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**N/A**

Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	**N/A**
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**N/A**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**September 5, 2003**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**April 24, 2003**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**July 28, 2003**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**September 15, 2003**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**August 30, 2003**
❖ Environmental Assessment – **See CMC review**	
• Categorical Exclusion *(indicate review date)*	**August 30, 2003**
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report) **See CMC review**	Date completed: **December 17, 2002** (**X**) Acceptable ( ) Withhold recommendation
❖ Methods validation – **Not completed at time of review**	( ) Completed (**X**) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**March 29, 2003**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

'02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bayer Pharmaceuticals Corporation	August 28, 2003
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(203) 812-5172	(203) 812-5029
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 400 Morgan Lane, West Haven, CT 06516	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-554

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
ciprofloxacin extended-release tablets	Cipro® XR

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride, monohydrate

CODE NAME (*If any*)
BAY o 9867 and BAY q 3939

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Extended-Release Tablets	1000 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Request for Information-Revised Phase IV Commitments

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

#21,804 NDA #19-537 (b) (4)
#25,173 NDA #19-847 DMF 10353 (b) (4) (b) (4)
IND #43,007 NDA #19-857
IND #61,331 NDA #20-780 DMF 8134 (b) (4)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER *(Specify)* Response to FDA Request for Information-Revised Phase IV Commitments

CERTIFICATION

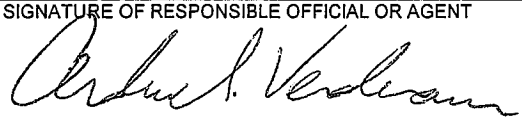
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Andrew S. Verderame Director, Regulatory Affairs	8/28/03

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
400 Morgan Lane West Haven, CT 06516	(203) 812-5172

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-554
Trade Name: Cipro® XR
Generic Name: Ciprofloxacin / Ciprofloxacin HCL
Strength: 1000mg tablets

Applicant: Bayer Pharmaceutical Corporation

Date of Application: October 29, 2002
Date of Receipt: October 29, 2002
Date of Filing Meeting: December 9, 2002
Filing Date: December 29, 2002

Indications requested: Complicated UTI and acute uncomplicated pyelonephritis

Type of Application: Full NDA _**X**_____ Supplement _____
(b)(1) _____**X**____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S____**X**___ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)_**3**_____
Other (orphan, OTC, etc.)_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES **X** NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
YES NO

If the application is affected by the application integrity policy (AIP), explain. N/A

User Fee Status: Paid _____**X**_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES__**X**_____ NO_____
User Fee ID#_**4407**___
Clinical data? YES ___**X**____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: **August 29, 2003**

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? **X** YES NO
- Form 356h included with authorized signature? **X** YES NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? **X** YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? **X** YES NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO **X** NA

- Patent information included with authorized signature? **X** YES NO

- Exclusivity requested? YES; If yes, _____years **X** NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? **X** YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? **X** YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES **X** NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:
  Waiver requested for all ages of pediatric population
- Field Copy Certification (that it is a true copy of the CMC technical section)? **X** YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? **X** YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: **61,331**

End-of-Phase 2 Meeting? **X** NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? **X** NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? **X** YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
X YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO **X** N/A

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO **X** N/A

Advisory Committee Meeting needed? YES, date if known _____ **X** NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO **X** N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? **X** YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? **X** YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? **N/A**

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO
If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 9, 2002

BACKGROUND
Cipro XR, 500mg, was approved for uncomplicated UTI and this NDA was submitted requesting two indications, complicated UTI and acute uncomplicated pyelonephritis. The strength of the tablets are 1000mg.

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Joette Meyer
Statistical:	Ruthanna Davi
Pharmacology/Toxicology:	Stephen Hundley
Chemist:	Dorota Matecka
Environmental Assessment (if needed):	
Biopharmaceutical:	Dakshina Chilukuri
Microbiology, clinical (for antimicrobial products only):	Pete Dionne
Project Manager:	Jouhayna Saliba

Per reviewers, all parts in English, or English translation? YES_**X**____ NO___

CLINICAL – File ____**X**_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO___ **X** _____

MICROBIOLOGY CLINICAL – File_____ **X** _____ Refuse to file_____

STATISTICAL – File _____ **X** _____ Refuse to file _____

BIOPHARMACEUTICS – File ____ **X** _____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ____ **X** _____

PHARMACOLOGY – File ___ **X** _____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File__ **X** ___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

____ **X** ___The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
_____ The application is unsuitable for filing. Explain why:

__Jouhayna Saliba_____
Regulatory Project Manager, HFD-590

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jouhayna Saliba
10/17/03 03:32:13 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: July 17, 2003

To: Robin Christoforides	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** (301) 827-2387

Subject: Information requested and discussed a the July 10, 2003 teleconference
Additional requests that have come up after the teleconference

Total no. of pages including cover:

Comments:

Document to be mailed: " YES ☑ NO

Dear Ms. Christoforides:

As per our teleconference from July 10th, for the organisms that appear in the table in the clinical studies section for which there are less than 10 patients listed, please articulate what information is available to support your inclusion in this table. The type of information that would be helpful may include, but is not limited to, the following:

1. Whether the immediate-release formulation of ciprofloxacin has this organism listed for the indication(s) of complicated UTI and/or AUP.

2. Information to support extrapolation of ciprofloxacin immediate release formulation efficacy data to support efficacy of the XR formulation against the organisms in question.

3. Information regarding the pathophysiology of complicated UTI and/or AUP and ciprofloxacin that could be used to support the position that immediate-release formulation efficacy data can be used to extrapolate that ciprofloxacin XR would have similar efficacy against the organisms in question.

4. Information from the literature that would indicate whether or not a change has been noted in ciprofloxacin's efficacy against the organism in question since the immediate-release formulation became available, in the indication of complicated UTI/AUP."

Following are the discussion items and recommendations brought up at the teleconference regarding the Monte Carlo report:

1. It appears that the FO method was used in the modeling and simulation. It is known that FOCE/INTERACTION method is preferable for a relatively dense data set. Please address why only FO was used.

2. In the simulation, according to the code, CL_{cr} of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renally impaired and severely renal impaired, respectively. This approach is considered to be inadequate. It is preferable to simulate with ranges of CL_{cr} values for normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment. Therefore, as a Phase IV commitment, please perform additional Monte-Carlo simulations to obtain estimates of ciprofloxacin systemic exposure after administration of the following regimens:

   - 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) mL/min)
   - 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4)-50 mL/min)

- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} (b) (4) (b) (4) mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} (b) (4) -50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CL_{cr} (b) (4) 120 mL/min)

3. The established relationship between clearance (CL) of intravenously administered ciprofloxacin and creatinine clearance (CL_{cr}) was used. However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of the orally administered Cipro IR tablet and use it for the purpose of modeling and simulations. We recommend that you re-develop the relationship between oral ciprofloxacin clearance and creatinine clearance (CL_{cr}) and compare with the previous results.

In addition, we would like to provide the following comments and requests, which came up after the July 10, 2003 teleconference.

We note that there is a differential rate of exclusion from the Cipro XR and Cipro BID treatment arms in Study 100275. We also note that in your table which details the reasons for exclusion from the Per Protocol analysis, that patients may not be categorized by the major reason for exclusion. For example, a patient in the category "No valid TOC urine culture" may have been excluded due to a "ciprofloxacin resistant pathogen" and yet there is also a category called "organism resistant to study drug". Therefore, we would like you to reclassify patients based upon the root cause for exclusion. Examples of exclusion categories which are acceptable to use include:

Organism resistant to study drug
Concomitant antimicrobial therapy
Exclusion/Inclusion criteria violation - provided that the specific violation is noted
Never received study medication
Discontinuation due to adverse event(s)
Consent withdrawn (please provide reason)
Investigator withdrawal of patient (please provide reason)
Insufficient therapeutic response
Lost to follow-up (please provide reason)
Death
TOC outside the 5-11 day window (please provide reason)

Examples of exclusion categories, which should not be used include:

Protocol violation
No valid TOC urine culture

Also, please provide your interpretation regarding any by-treatment group imbalances in the rate of exclusion.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2387

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/s/

Jouhayna Saliba
7/17/03 11:13:22 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 28, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Chemistry comments

Total no. of pages including cover: 4

Comments:

Document to be mailed: ❑ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: May 28, 2003

TO: Andrew Verderame
Director, Regulatory Affairs

ADDRESS: Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172

FAX: 203-812-5029

FROM: Jouhayna Saliba

SUBJECT: NDA 21-554 (ciprofloxacin extended-release tablets, 1000 mg)

Please address the following CMC comments regarding your NDA:

1. Please submit general information for ciprofloxacin hydrochloride drug substance in the NDA (i.e. nomenclature, structure, and physicochemical properties). This should include information on (b) (4) and description of how (b) (4) in the drug substance.

2. Please submit general information for Ciprofloxacin (b) (4) drug substance in the NDA (i.e. nomenclature, structure, and physicochemical properties). This should include detailed information regarding (b) (4) of Ciprofloxacin (b) (4)

3. Please submit the specification for Ciprofloxacin (b) (4) that reflects revisions in the particle size distribution acceptance criteria and loss on drying previously agreed to for CIPRO XR, 500 mg (NDA 21-473).

4. Please provide in the NDA a specification (list of tests, acceptance criteria and analytical procedures) for ciprofloxacin hydrochloride drug substance.

5. Please include the test for water content as part of the specification for the drug product, CIPRO XR tablets, 1000 mg.

6. Please provide the following information with regards to the container/closure systems proposed for marketing of CIPRO XR tablets, 1000 mg:

   a) list of all materials and their respective DMFs that will be used in the commercial packaging components only;

   b) results of the physicochemical testing conducted on all the packaging components as per USP <661> (including light transmission) and moisture vapor permeation as per USP <671>;

   c) results of the (b) (4) testing for unit-dose packaging components;

   d) confirmation that all packaging components comply with the appropriate sections of CFR.

7. Please provide updated ((b) (4) months, if available) stability results for the primary stability batches and any available additional data for other supplemental batches included in the stability program.

8. Please provide the results of the statistical analysis studies performed on at least three NDA stability batches of the drug product, using the shelf-life-limiting attribute.

If you have any questions, please contact me at (301) 827-2387.

_____

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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/s/

Jouhayna Saliba
5/28/03 02:19:27 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 22, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Comments regarding report from study 100275 and the proposed PI dated 05/03

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: May 22, 2003

TO: Andrew Verderame
Director, Regulatory Affairs

ADDRESS: Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172

FAX: 203-812-5029

FROM: Jouhayna Saliba

APPLICATION: NDA 21-554

SUBJECT: Study 100275 and the proposed PI dated 5/03

- We note from the report of study BAY-Q3939-100275 that a significant treatment-by-infection-type interaction is present for the analysis of the primary efficacy endpoint (i.e., bacteriologic response at the test-of-cure visit). Internal analyses have indicated that while not statistically significant, trends towards the same type of interaction are also observed with the bacteriologic response at the follow-up visit. Please comment on the appropriateness of combining eradication rates for AUP and cUTI patients, in light of the observation that the treatment effect within each stratum may be different.

- It has come to our attention that the revised proposed package insert (dated 5/03) for uUTI and cUTI is missing information currently in the approved uUTI package insert which has not been indicated with a strikeout. Specifically, in the approved uUTI package insert, under CLINICAL STUDIES, Uncomplicated Urinary tract Infections (acute cystitis), there is a table containing eradication and clinical success rates in the clinical trial. The fourth line in the table is "Bacteriologic Eradication at TOC", the primary endpoint of the study. Eradication rates are shown for both Cipro XR and Cipro (b) (4) [i.e., 188/199 (94.5%) and 209/223 (93.7%), respectively]. In the proposed package insert (dated 5/03) these numbers have been omitted.

Please resubmit the proposed package insert with these numbers in the uUTI table reinserted. In addition, if you utilize a table for cUTI and AUP infections (study 100275), it should mirror the uUTI table.

If you have any questions, please contact me at (301) 827-2387.

_____

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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/s/

Jouhayna Saliba
5/22/03 02:57:19 PM
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150 page(s) has been Withheld in Full as Draft Labeling (CCI/TS) immediately following this page

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Comments on draft report submitted February 20, 2003

Total no. of pages including cover: 4

Comments:

Document to be mailed: ❑ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: April 3, 2003

TO: Andrew Verderame
Director, Regulatory Affairs

ADDRESS: Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172

FAX: 203-812-5029

FROM: Jouhayna Saliba

APPLICATION: NDA 21-554

SUBJECT: Comments on the draft report submitted February 20, 2003

We refer to your submission dated February 20, 2003. We would like to thank you for providing the draft report for the Monte-Carlo simulations for various doses/durations/formulations of ciprofloxacin products in patients with varying degrees of renal insufficiency. Please address the following in your final report:

- Why was data from Study D84-024-2 (Ref. NDA 19-537) not used for simulations? This study has data for 250, 500 and 750 mg dose strengths in patients with various degrees of renal insufficiency.
- Please provide spaghetti plots for individual patient plasma concentration-time data generated using the simulations.
- Do you plan to submit additional internal/external validation results (prediction errors) as part of model validation?
- Please provide raw data of the IR formulations from the Renal Impairment studies (Study # 0622, 0953 and 0164) as part of the final report.
- Please refer to the Clinical Pharmacology Guidance on Population Pharmacokinetics (http://www.fda.gov/cder/guidance/index.htm) for details on submitting raw data used in the analysis.

If you have any questions, please contact me at (301) 827-2387.

_____

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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/s/

Jouhayna Saliba
4/3/03 01:26:04 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 7, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** (301) 827-2387

Subject: request CRF

Total no. of pages including cover: 5

Comments:

Document to be mailed: ❑ YES ☑ NO

NDA 21-554
CIPRO® XR

Dear Mr. Verderame:

We refer to NDA 21-554, submitted October 29, 2002. Please provide the Case Report Forms for the following 10% random sample. Also, please include the microbiology data in these CRFs. If any of the CRFs for patients included in the sample have been previously submitted as part of the original NDA, please let us know where to find these patients.

You may choose to submit the above request either electronically or in paper. However, we would appreciate a paper copy.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2387

Patient Number (Protocol 100275)

100275-002-002028
100275-004-004002
100275-004-004005
100275-006-006012
100275-006-006016
100275-006-006022
100275-006-006024
100275-006-006029
100275-015-015021
100275-017-017005
100275-019-019001
100275-019-019011
100275-019-019014
100275-020-020001
100275-025-025005
100275-025-025011
100275-025-025015
100275-025-025018
100275-025-025027
100275-025-025028
100275-026-026026
100275-029-029041
100275-031-031012
100275-031-031035
100275-034-034001
100275-036-036009
100275-037-037006
100275-041-041027

100275-042-042003
100275-042-042004
100275-042-042012
100275-042-042017
100275-042-042035
100275-042-042037
100275-042-042050
100275-042-042058
100275-045-045009
100275-045-045019
100275-045-045022
100275-045-045026
100275-045-045039
100275-048-048014
100275-048-048015
100275-048-048017
100275-048-048019
100275-048-048028
100275-048-048033
100275-048-048038
100275-049-049011
100275-049-049016
100275-049-049021
100275-049-049026
100275-049-049047
100275-050-050002
100275-050-050010
100275-052-052006
100275-052-052010
100275-053-053004
100275-053-053010
100275-053-053014
100275-053-053015
100275-053-053025
100275-059-059013
100275-059-059022
100275-059-059024
100275-059-059027
100275-059-059032
100275-062-062008
100275-063-063003
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100275-068-068003
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100275-073-073022
100275-073-073032

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100275-076-076008
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100275-082-082025
100275-086-086003
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100275-095-095003
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100275-095-095027
100275-097-097001
100275-101-101007
100275-102-102001
100275-102-102014
100275-102-102019
100275-116-116001
100275-118-118057
100275-120-120005
100275-130-130001
100275-138-138005
100275-139-139009
100275-142-142024
100275-148-148001
100275-148-148003
100275-148-148012
100275-148-148019
100275-148-148028
100275-160-160001
100275-160-160003
100275-205-205005
100275-205-205008
100275-207-207059
100275-209-209006
100275-209-209013
100275-209-209015
100275-209-209026
100275-211-211007

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/s/

Jouhayna Saliba
2/7/03 03:23:09 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

2. TELEPHONE NUMBER *(Include Area Code)*

(203) 812-5172

3. PRODUCT NAME
Cipro XR

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N #21-554

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4406

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, on reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
ville, MD 20852-1448

and

Food and drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew L. Vanderslice	Director, Regulatory Affairs	10/29/02

FORM FDA 3397 (3/01)