CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-473

Trade Name: Cipro XR

Generic Name: Ciprofloxacin extended release

Sponsor: Bayer Healthcare Pharmaceuticals Inc.

Approval Date: December 13, 2002

Indications: For the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms such as *Escherichia coli, Proteus mirabilis, Enterococcus faecalis, or Staphylococcus saprophyticus.*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-473

Bayer Corporation
Attention: Andrew Verderame
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

Please refer to your new drug application (NDA) dated March 4, 2002, received March 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® XR (ciprofloxacin extended-release tablets), 500 mg.

We acknowledge receipt of your submissions dated:

April 9, 2002
April 11, 2002
April 12, 2002
April 22, 2002
April 23, 2002
May 6, 2002
May 7, 2002
May 8, 2002
May 9, 2002
June 28, 2002
July 12, 2002
July 18, 2002 (3)
August 7, 2002
September 10, 2002
September 20, 2002
November 15, 2002 (2)
November 21, 2002
November 22, 2002
November 26, 2002 (4)
December 4, 2002 (2)
December 6, 2002 (4)
December 12, 2002 (2)

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

We have 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 patient package insert submitted December 12, 2002) and submitted labeling (immediate container and carton labels submitted September 20, 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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-473**." 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 December 12, 2002. These commitments are listed below.

1. Provide confirmative evidence of CIPRO XR efficacy in treating uncomplicated urinary tract infections caused by *S. saprophyticus.*

Protocol Submission:	July 1, 2003
Study Start:	October 1, 2003
Final Report Submission:	December 31, 2004

2. Provide an annual update on CIPRO XR usage patterns for the first two years of product availability; with the submission dates being no later than February 28, 2004 and February 28, 2005 respectively.

Submit any clinical protocols for these studies to your IND for this product. Submit any 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."**

The text in italics below addresses the application of FDA's Pediatric Rule at 21 CFR 314.55 to this NDA. The Pediatric Rule has been 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. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we conclude the following:

For uncomplicated urinary tract infections (acute cystitis) caused by Escherichia coli, Proteus mirabilis, Enterococcus faecalis, or Staphylococcus saprophyticus.

- *We are deferring submission of pediatric studies for pediatric patients ages 0-16 years until December 31, 2008.*

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to 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

Please submit one market package of the drug product when it is available.

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

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

If you have any questions, call Jouhayna Saliba, 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

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

12/13/02 02:10:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

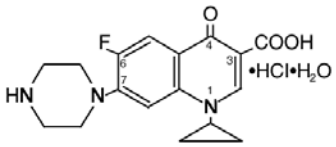
LABELING

CIPRO® XR
(ciprofloxacin* extended-release tablets)

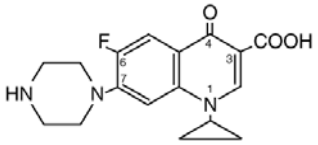
Final uUTI PI **12/12/02**

DESCRIPTION

CIPRO® XR (ciprofloxacin* extended-release 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. It is provided as a mixture of the monohydrate and the sesquihydrate. The empirical formula of the monohydrate 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 Tablets are available as 500 mg (ciprofloxacin equivalent) tablets 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). 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 ciprofloxacin immediate-release BID treatment, which is approved for the treatment of uncomplicated urinary tract infections, the C_{max} of CIPRO XR 500mg once daily is higher, while the AUC over 24 hours is equivalent.

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

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)

§ 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; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L.

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. The total drug exposure attained with 500 mg CIPRO XR is similar to or less than that achieved with a single dose of 500 mg immediate-release ciprofloxacin, which is approved for use in patients with severe renal impairment. (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, Drug Interactions** and **Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

Omeprazole: When CIPRO XR was administered as a single 1000 mg dose (twice the recommended daily 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. (See **PRECAUTIONS, Drug Interactions.)** These differences are not considered clinically significant.

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
Proteus mirabilis

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	*Klebsiella pneumoniae*
Citrobacter freundii	*Morganella morganii*
Edwardsiella tarda	*Proteus vulgaris*
Enterobacter aerogenes	*Providencia rettgeri*
Enterobacter cloacae	*Providencia stuartii*
Klebsiella oxytoca	*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, 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

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, and *Staphylococcus* species:

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

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 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

INDICATIONS AND USAGE

CIPRO XR is indicated solely for the treatment of uncomplicated urinary tract infections (acute cystitis) 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].

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

THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING INFECTIONS OTHER THAN UNCOMPLICATED URINARY TRACT INFECTIONS HAVE 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. This difference is not considered clinically

significant. (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 4- and 6-fold greater than the 500 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 twice the maximum recommended daily human dose of 500 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 (1.9 times the highest recommended daily human dose of 500 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 (1.4 and 0.7 times the maximum daily human dose of 500 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 clinical studies with immediate-release ciprofloxacin, no differences in safety or effectiveness were observed between elderly and young patients. Ciprofloxacin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. However, no significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take CIPRO XR. The total drug exposure and maximum serum concentrations attained with CIPRO XR are similar to or less than the corresponding values achieved with 500 mg immediate-release ciprofloxacin, which is approved for use in renally impaired patients. Therefore, no reductions in dosage are required. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTATION.**)

ADVERSE REACTIONS

A clinical trial enrolled 905 ciprofloxacin treated patients, of whom 444 patients received the CIPRO XR 500 mg QD dose and 447 patients received the CIPRO 250 mg BID dose. Most adverse events reported (93.5%) were described as mild to moderate in severity and required no treatment. CIPRO XR was discontinued due to adverse reactions thought to be drug-related in 0.2% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of CIPRO XR treated patients were nausea (3%) and headache (2%).

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, photosensitivity reaction

CARDIOVASCULAR: migraine

DIGESTIVE: anorexia, constipation, diarrhea, dyspepsia, flatulence, thirst, vomiting

CENTRAL NERVOUS SYSTEM: depersonalization, dizziness, hypertonia, incoordination, somnolence

SKIN/APPENDAGES: maculopapular rash, pruritus, rash, skin disorder, vesiculobullous rash

SPECIAL SENSES: taste perversion

UROGENITAL: dysmenorrhea, vaginal candidiasis, 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):
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, depression, diplopia, 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, hematuria, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic necrosis, hiccup, hyperpigmentation, hypertension, hypotension, ileus, insomnia, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lymphadenopathy, malaise, manic reaction, mouth dryness,

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, syncope, tachycardia, taste loss, tendinitis, tendon rupture, tinnitus, toxic epidermal necrolysis, toxic psychosis, tremor, 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), weakness.

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. 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

In uncomplicated urinary tract infections (acute cystitis), the recommended dosage of CIPRO XR is 500 mg once daily for 3 days. CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable.

DOSAGE GUIDELINES

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500 mg	Q24h	3 Days

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. 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 ciprofloxacin. The tablet is coded with the word "BAYER" on one side and "C500 QD" on the reverse side.

	NDC Code
Bottles of 50	0026-8889-50
Bottles of 100	0026-8889-51

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 bacteriological eradication 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
Clinical Response at TOC (n/N)*	189/199 (95.0%)	204/223 (91.5%)
	CI [-1.1%, 8.1%]	
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%)

* n/N = patients with pathogen eradicated /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).

References: 1. NCCLS, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000. 2. NCCLS, Performance Standards for Antimicrobial Disk Susceptibility Tests-Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.

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 simple urinary tract infections (also known as cystitis or bladder infections). It should not be used to treat infections other than simple urinary tract 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 simple urinary tract infections. CIPRO XR has been shown in clinical trials to be effective in the treatment of simple 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 Tablets are available in a 500 mg strength.

How and when should I take CIPRO XR?

CIPRO XR should be taken once a day for three (3) days 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 and headache. Antibiotics of the quinolone class may also cause diarrhea, vomiting, rash, and abdominal pain/discomfort. If diarrhea persists, call your health care professional.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

MEDICAL REVIEW(S)

MOR 21- 473
CIPRO XR (formerly known as Cipro (b) (4) and Cipro (b) (4))

EXECUTIVE SUMMARY NDA 21- 473
Uncomplicated Urinary Tract Infections
CIPRO XR (formerly known as Cipro (b) (4) and Cipro (b) (4))

Background: Bayer submitted NDA 21-473 on March 4, 2002. The requested indication was for the use of Cipro XR in the treatment of uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli,* (b) (4), *Proteus mirabilis, Staphylococcus saprophyticus,* and *Enterococcus faecalis".*

The proposed dose is one 500 mg tablet PO QD for 3 days. The indication as it appears in the proposed label is as follows:

"CIPRO XR is indicated solely for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms as listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli,* (b) (4) *Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus.*

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

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 Tablets 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".

Ciprofloxacin XR tablets are a new modified release formulation developed by Bayer in 500 mg and 1000 mg (ciprofloxacin equivalent) strengths. The 500 mg tablet is intended for the treatment of uncomplicated urinary tract infections (the subject indication of this NDA) and the 1000 mg tablet is intended for the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis.

Currently, the oral quinolone antimicrobials that are approved for the treatment of uncomplicated urinary tract infection include:

Ciprofloxacin: For uncomplicated urinary tract infection caused by *Escherichia coli* or *Staphylococcus saprophyticus.*

Floxin®: For uncomplicated urinary tract infection caused by *Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis or Pseudomonas aeruginosa.*

Maxaquin®: For uncomplicated urinary tract infection caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Staphylococcus saprophyticus.*

Noroxin®: For uncomplicated urinary tract infection caused by *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Citrobacter freundii, Enterobacter* aerogenes, *Enterobacter cloacae, Proteus vulgaris, Streptococcus agalactiae.*

Penetrex®: For uncomplicated urinary tract infection caused by *Escherichia coli, Staphylococcus epidermidis* and *Staphyloccus saprophyticus.*

Tequin®: Uncomplicated UTI (cystitis) due to *Escherichia coli, Proteus mirabilis,* or *Klebsiella pneumoniae.* (single dose)

The clinical data were derived from one phase III, prospective, active-controlled, randomized, double blind, multicenter study (Study 100346 Cipro XR 500 mg PO QD x 3 days vs. Cipro 250 mg PO BID x 3 days) conducted in the United States in adult female patients (ages 18 to 65 years) with uncomplicated urinary tract infections. 58 of 63 outpatient centers enrolled patients.

Pivotal Study 100346

Dates	Design	Treatment/ Dose[a]	Duration of Rx	# Patients Enrolled Per Treatment Arm	Age[b] Range (Mean) years	Race % B/W/O[b,c]
3/7/01 to 10/22/01	Active-Controlled, Randomized, Double-Blind, Multicenter	Cipro XR 500 mg PO QD	3 days	452	18-79 (35.1)	10/78/12
		Cipro® 250 mg PO BID	3 days	453	18-76 (34.7)	8/80/12

a QD = once daily, BID = twice daily
b Randomized population
c B = Black, W = White, O = Other

905 women were enrolled and 891 (444 in the Cipro XR group and 447 in the Cipro® BID group) received at least one dose of study drug and were included in the valid for safety population. 422 patients (199 in the Cipro XR group and 223 in the Cipro® BID group) fulfilled the criteria for the valid for efficacy population. The treatment groups were similar with respect to baseline demographic variables and infection characteristics. The primary efficacy variable was microbiologic outcome at the test-of-cure (TOC) visit. Secondary efficacy variables included clinical response at the TOC, as well as

microbiologic and clinical outcomes at the late follow-up visit. Analyses were performed on the subset of valid patients and on the ITT population.

Cipro XR for 3 days was non-inferior to Cipro® BID for 3 days with respect to the primary and secondary efficacy parameters.

Microbiologic and Clinical Outcome Valid for Efficacy Population

	Ciprofloxacin XR 500 mg PO QD x 3 days	**Ciprofloxacin 250 mg PO BID x 3 days**	**FDA 95% CI (with CCF*) Δ = ±10**
Microbiologic Eradication			
TOC (Day +4 to +11)	188/199 (94.5%)	209/223 (93.7%)	- 4.2%. 5.7%
Late Follow-Up (Day +25 to +50)	151/199 (75.9%)	165/223 (74%)	- 6.9%. 10.6%
Clinical Cure			
TOC (Day +4 to +11)	189/198 (95.5%)	204/220 (92.7%)	- 2.2%, 7.7%
Late Follow-Up (Day +25 to +50)	161/181 (89%)	187/216 (86.6%)	- 4.6%, 9.3%

* = continuity correction factor

Cipro XR was effective against infections caused by the predominant group of pathogens causing uncomplicated urinary tract infections.

Microbiologic Outcome of Original Causative Organism at the TOC Valid for Efficacy Population

	Cipro XR N = 199 (204 Original Organisms)	**Cipro®BID N = 223 (239 Original Organisms)**
	Eradication N (%)	**Eradication N (%)**
Escherichia coli	156/160 (97.5%)	176/181 (97%)
Enterococcus faecalis	10/11 (91%)	17/21 (81%)
Klebsiella pneumoniae	7/9 (78%)	11/14 (79%)
Proteus mirabilis	11/12 (92%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83%)	7/7 (100%)
Enterobacter aerogenes	2/2 (100%)	3/3 (100%)
Enterobacter cloacae	2/2 (100%)	2/2 (100%)
Citrobacter koseri	-	2/2 (100%)
Klebsiella ornithinolytica	-	2/2 (100%)
Proteus vulgaris	1/1 (100%)	-
Stenotrophomonas maltophilia	1/1 (100%)	-

***bold** type denotes requested pathogens

In conclusion, Cipro XR at a dose of 500 mg PO once daily for 3 days was effective in the treatment of uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*, *Proteus mirabilis*, and *Enterococcus faecalis*.

Cipro XR and Cipro®BID, both given for 3 days for the treatment of uncomplicated UTI, exhibited similar safety profiles. No clinically meaningful differences were found between the two formulations of ciprofloxacin.

The incidence of AEs in patients treated with Cipro XR was 27%. The body as a whole was the body system with the highest percentage (11%) of AEs. Most (93.5%) AEs were mild to moderate in intensity. No single AE was considered severe in more than 2 patients. Adverse events occurring in at least 2% of patients treated with Cipro XR were headache (4%) and nausea (4%).

Drug-related AEs were reported in 10% of patients, with nausea (3%) and headache (2%) being the only two drug-related AEs occurring in 1% or more of patients. Only 1 (flatulence) of 45 drug-related AEs in the Cipro XR group remained unchanged. All other drug-related AEs either resolved or improved.

No patient deaths occurred during the study. Two patients (<1%) were withdrawn early due to an AE and 6 patients (1%) experienced SAEs. The incidence of laboratory test abnormalities, especially clinically significant abnormalities, was low. Descriptive statistics of changes in laboratory test results from baseline did not show any trend that appeared to be uniquely associated with Cipro XR.

Based on the safety profile of Cipro XR from the pivotal study, the additional safety information available from clinical pharmacology studies, and the long-term clinical experience with ciprofloxacin it was concluded that Cipro XR given as 500 mg every 24 hours for 3 days is safe for use for the treatment of uncomplicated urinary tract infections (acute cystitis).

Special Populations:
In the February 13, 2001 End of Phase II meeting, an agreement was reached between the FDA and the applicant that there did not need to be special population studies for this NDA (hepatic, renal impairment, elderly) based on data already established with Cipro ®
.

MO Recommendation:

Approval of Cipro XR 500 mg QD x 3 days to treat uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli, Enterococcus faecalis,* and *Proteus mirabilis.* There were an insufficient number of uncomplicated urinary tract infections due to *Staphylococcus saprophyticus* and *Klebsiella pneumoniae* to support the indication for treatment of these organisms.

Medical Officer's Review of NDA 21- 473
Uncomplicated Urinary Tract Infections
CIPRO XR (formerly known as Cipro (b) (4) and Cipro (b) (4)

Indication: Ciprofloxacin XR 500 mg tablets are indicated in the treatment of uncomplicated urinary tract infection (acute cystitis) caused by *Escherichia coli*, (b) (4), *Proteus mirabilis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis* in women.

I. Introduction and Background

A. Applicant, Drug Established and Proposed Trade Names, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Applicant: Bayer Pharmaceutical Division

Address: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Date of Submission: March 4, 2002
CDER Stamp date: March 4, 2002
Date Submission received by reviewer: April 8, 2002
Date Review Begun: April 16, 2002
Date Review Completed: September 14, 2002

Drug Name: Ciprofloxacin Hydrochloride and Ciprofloxacin

Proprietary Name: CIPRO® (b) (4) (proposed)

Pharmacologic Category: Fluoroquinolone

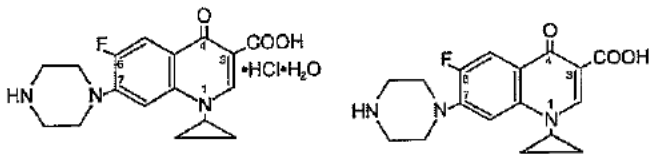
Chemical Name: The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base).

Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1 piperazinyl)-3 quinolinecarboxylic acid hydrochloride monohydrate.

Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

Molecular formula and weight: $C_{17}H_{18}FN_3O_3$ (385.8) and $C_{17}H_{18}FN_3O_3$ (331.4).

Chemical structure:



Dosage Form: Tablets

Route of Administration: Oral

Strengths: 500 mg tablets

Proposed Indications and Usage:
(As per the proposed label)

CIPRO XR is indicated solely for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms as listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli,* (b) (4) *Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus.*

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

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 Tablets 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.

Related IND and NDAs:

IND 21,804, IND 25,173, IND 43,007, IND 61,331
NDA 19-537, NDA 19-847, NDA 19-857, NDA 20-780

Materials Reviewed:

Electronic Submission March 4, 2002
CDROM with CRFS April 12, 2002
CDROM with submission April 4, 2002
Email response to MO queries April 9,11, and 22, 2002
CDROM with microbiology data April 22, 2002

Email response to FDA queries May 7, 8, and 9, 2002
CDROM with AE data May 9, 2002

Abbreviations:

CRF = Case Report Form
TMP/SMX = Trimethoprim sulfamethaxazole
AE = Adverse Event
EOT = End of Therapy
ITT = Intent to Treat
EP = Evaluable Population
TOC = Test of Cure
CUTI = Complicated Urinary Tract Infection

Note on fonts: This review is written in Times New Roman 12. Arial is used for direct quotes from the applicant's submission.

B. State of Armamentarium for Indication(s):

Quinolone Antimicrobial Agents Currently Approved for the Uncomplicated UTI Indication:

Ciprofloxacin: For uncomplicated urinary tract infection caused by *Escherichia coli* or *Staphylococcus saprophyticus*.

Floxin®: For uncomplicated urinary tract infection caused by *Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis or Pseudomonas aeruginosa.*

Maxaquin®: For uncomplicated urinary tract infection caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Staphylococcus saprophyticus.*

Noroxin®: For uncomplicated urinary tract infection caused by *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Citrobacter freundii, Enterobacter* aerogenes, *Enterobacter cloacae, Proteus vulgaris, Streptococcus agalactiae.*

Penetrex® : For uncomplicated urinary tract infection caused by *Escherichia coli, Staphylococcus epidermidis* and *Staphyloccus saprophyticus.*

Tequin®: Uncomplicated UTI (cystitis) due to *Escherichia coli, Proteus mirabilis,* or *Klebsiella pneumoniae.*

Current Literature:

Uncomplicated urinary tract infections are among the most common bacterial infections in women, accounting for an estimated 8 million episodes per year in the United States as well as significant morbidity and health care costs[1].

The spectrum of pathogens causing these infections is narrow and includes primarily *Escherichia coli* that accounts for 75% to 90% of infections, followed by *Staphylococcus saprophyticus* that accounts for 5% to 15%, and enterococci and other gram-negative rods, such as *Klebsiella pneumoniae* and *Proteus mirabilis* that account for the remaining 5% to 10%[2]. Evidence-based treatment guidelines for acute uncomplicated urinary tract infections have recently been developed by the Infectious Diseases Society of America (IDSA)[1]. A 3-day course of antimicrobial therapy is the most effective and best-tolerated regimen. Single-dose therapy is less effective than 3-day therapy. Seven-day regimens are not more effective than 3-day therapy, but they result in additional adverse events[3]. For cystitis, the IDSA guidelines recommend TMP-SMX as initial therapy in regions where the prevalence of resistance to this antibiotic does not exceed 10% to 20%, and that ongoing surveillance be conducted to monitor changes in susceptibility of uropathogens. Fluoroquinolones are recommended in areas with high prevalence of resistance to TMP-SMX or in patients with risk factors for resistance.

Resistance among uropathogens to TMP-SMX and beta-lactams has been increasing over the past several years [2]. In a study of women with acute uncomplicated cystitis, Masterton and Bochsler demonstrated that patients infected with uropathogens resistant to TMP-SMX achieved only a 50% cure rate when treated with TMP-SMX, compared to an 86% cure rate for all women in the TMP-SMX group[4]. In another study, McCarty and colleagues found that the microbiologic success rate was 50% and the clinical cure rate was 60% among women infected with a uropathogen resistant to TMP-SMX who had been randomized to TMP-SMX treatment[5]. This supports the IDSA guidelines of using a fluoroquinolone in treating cystitis in areas with resistance to TMP-SMX ≥10% to 20%.

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[1] Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999;29(4):745-58.

[2] Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. Ann Intern Med 2001;135(1):41-50.

[3] Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis 2001;183(Suppl 1):S1-4.

[4] Masterton RG, Bochsler JA. High-dosage co-amoxiclav in a single dose versus 7 days of co-trimoxazole as treatment of uncomplicated lower urinary tract infection in women. J Antimicrob Chemother 1995;35(1):129-37.

[5] McCarty JM, Richard G, Huck W, Tucker RM, Tosiello RL, Shan M, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Ciprofloxacin Urinary Tract Infection Group. Am J Med 1999;106(3):292-9.

In the United States and much of Europe, resistance in uropathogens to ciprofloxacin remains rare despite at least 14 years of use[6] [7].

Background and Definitions:

There are two marketed oral formulations of ciprofloxacin currently available: Cipro® Tablets and Cipro® Oral Suspension. Cipro® Tablets are available in 100 mg, 250 mg, 500 mg, and 750 mg strengths. Cipro® Oral Suspension is available in 5% and 10% strengths. Both of these formulations are approved in the US for the treatment of several types of infections caused by susceptible strains of certain designated microorganisms, including "Acute Uncomplicated Cystitis" in females (100 mg (AP 1996) or 250 mg twice daily for 3 days (AP 10/87) and "Urinary Tract Infections" (NDA 19-537 AP 10/87)

Cipro XR tablets are a new modified release formulation developed by Bayer in 500 mg and 1000 mg (ciprofloxacin equivalent) strengths. The 500 mg tablet is intended for the treatment of uncomplicated urinary tract infections (the subject indication of this NDA) and the 1000 mg tablet is intended for the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis.

The 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. PK studies indicate that the modified-release tablets result in a higher C_{max} and an equivalent AUC when compared with Cipro® Tablets for the same total dose of ciprofloxacin (e.g., Ciprofloxacin XR 500 mg tablets compared to Cipro® Tablets given as 250 mg twice daily. As per the applicant, "High peak levels of Ciprofloxacin XR should result in rapid bacterial killing. With regard to urine concentrations, significantly higher ciprofloxacin concentrations were found with Ciprofloxacin XR as compared with the corresponding dose of Cipro ® for the first 12 hours postdose, which may potentially provide improved urine bactericidal activity".

In accordance with the 7/22/1998 "Uncomplicated Urinary Tract Infections Developing Antimicrobial Drugs for Treatment" Draft Guidance for Industry document issued by ODE IV[8], the definition of an acute uncomplicated UTI or cystitis is "A clinical syndrome in women characterized by dysuria, frequency, and/or urgency in combination with pyuria and bacteriuria. There is no known underlying renal or urologic dysfunction or obstruction".

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[6] Sahm DF, Thornsberry C, Kelly LJ, Jones ME, Karlowsky JA. In vitro activities of commonly used antibiotics against prevalent uropathogens: implications for empiric therapy. Infect Urol 2001;14(3):59-67.

[7] Karlowsky JA, Jones ME, Thornsberry C, Critchley I, Kelly LJ, Sahm DF. Prevalence of antimicrobial resistance among urinary tract pathogens isolated from female outpatients across the US in 1999. Int J Antimicrob Agents 2001;18(2):121-7.

[8] US Food and Drug Administration. Guidance for Industry. Uncomplicated Urinary Tract Infections - Developing Antimicrobial Drugs for Treatment. Rockville, Md; 1998.

In order to obtain this indication, it is suggested that one statistically adequate and well-controlled multicenter trial be carried out that establishes safety and effectiveness (i.e., similar or superior effectiveness to an approved product). Although, generally, the primary effectiveness parameter in this study should be microbiologic outcome at 5 to 9 days after the cessation of therapy, the study should establish the general correlation between clinical cure and bacterial eradication in these patients. In addition, the above should be accompanied by adequate microbiologic and PK/PD data. An alternative is the submission of 2 large trials or the submission of efficacy data for the complicated urinary tract infection indication in conjunction with one uncomplicated UTI trial. In this case pathogens listed in the (b) (4) should be incorporated to the uncomplicated UTI indication as clinically indicated.

For a further review of the guidance, the reader is referred to the FDA web site.

Medical Officer's Comment: *The sponsor submitted a single Phase III multicenter, statistically adequate and well-controlled trial for the uncomplicated UTI indication in conjunction with supportive microbiologic and PK/PD studies including blood and urine samples obtained from 71 patients to measure plasma and urine concentrations of ciprofloxacin. These samples were drawn on day 2 or 3 of study drug treatment. 37/ 71 patients were randomized to the Cipro XR group. The applicant is also submitting an SNDA for the CUTI indication that could support the uncomplicated indication if necessary.*

From the standpoint of trial design, the pivotal trial was designed in accordance with the guidance documents. The comparator regimen ciprofloxacin 250 mg PO BID for 3 days is approved for the indication.

The primary efficacy parameter in accordance with the 1998 FDA Draft Guidance for Industry is microbiologic outcome at 5 to 9 days after the end of study drug treatment. This window was expanded by the applicant to 4 to 11 days after the end of study drug treatment prior to study unblinding, to include more data in the analysis. When queried about this widening of the "evaluability window", the applicant informed the MO that 26 patients were added to the evaluable population and of these 13 were added from day 4.

The MO elected to accept this change because the study was still appropriately powered and non-inferiority was proven with and without these subjects. Additionally the half-life of Cipro XR is 6.6 ± 1.4 hours. A post-antibiotic effect has been demonstrated for ciprofloxacin with a duration of one to three hours against Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus and Enterococcus. faecalis[9]*. These factors allow an efficacy analysis on day +4 for this formulation without establishing a broader regulatory precedence.*

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[9]. Lagast, H., M. Husson, J. Klasterski. 1985. Bacterial Activity of Ciprofloxacin in serum and Urine Against *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus*, and *Streptococcus faecalis*. J. Antimicrob. Chemother. 16:341-347.

Table 1
Microbiologic Efficacy with and without day 4 subjects at the TOC

	Cipro XR	Cipro® BID	FDA 95% CI with CCF
With Day + 4 Patients	188/199 (94.5%)	209/223 (93.7%)	- 4.2%. 5.7%
Without Day + 4 Patients	183/194 (94.3%)	201/215 (93.5%)	-4.3%, 5.9%

C. Important Milestones in Product Development

Regulatory Background:

- November 28, 2000: Pre IND meeting
- November 29, 2000: IND 61,331 for Cipro® (Ciprofloxacin) Modified-Release Tablets submitted (protocol 100346 included)
- February 13, 2001: End of Phase II meeting:

The results of the Phase I studies of the MR versus IR tablets, and subsequent PK/PD calculations were presented. The FDA had concerns that the MR and IR formulations are not bioequivalent according to strict interpretation of guidelines and that diminished plasma levels at the end of the dosing interval may impact efficacy. The FDA informed the sponsor that clinical trials for all indications desired are necessary in order to demonstrate clinical effectiveness to validate the PK/PD results. It was agreed that there did not need to be special population studies in the NDA (hepatic, renal impairment, elderly) based on data already established with Cipro ® .

FDA agreed to accept one uncomplicated UTI trial and one complicated UTI trail for each indication being sought. However a delta of 10%, was strongly suggested. The FDA did not agree with Bayer's original proposed NDA submission plan to submit the NDA with uncomplicated UTI (b) (4) (b) (4) (b) (4). An agreement was reached on 3/1/01 that 2 separate NDAs for the uncomplicated UTI and complicated UTI indications would be submitted.

- January 15, 2002: Pre – NDA meeting.

FDA agreed that a meeting within 2 months after the NDA submission would occur to discuss the results of the label comprehension study, Bayer's proposed trade name, and risk management strategies. DDMAC and OPDRA would also be invited. FDA stated that the label comprehension study results would be carefully examined.

FDA stated that an assessment of Cipro XR in CUTI will be required as part of the uncomplicated UTI approval process. The Agency commented that the CUTI study will

be carefully reviewed for the quality of the CUTI patients enrolled, to ensure that there are adequate numbers of true CUTI patients treated with Cipro XR.

Bayer informed the Agency that the development of a pediatric Ciprofloxacin (b) (4) formulation is not feasible, and that it is Bayer's intention to include the relevant information gathered from the ongoing pediatric trials with the approved ciprofloxacin formulations into the package insert for the once-daily product. The Agency stated that the NDA for Cipro XR should contain a request for deferral of pediatric studies until the results of any ongoing pediatric studies are completed.

Bayer advised the Agency that the product was planned to be packaged in bottles only (b) (4)

The Agency stated that ultimate approval of the product might come with a postmarketing commitment to assess whether the product is being used appropriately.

D. Other Relevant Information

List of Currently Approved Indications: None

Cipro XR (500 mg) has not been approved for marketing in any country and has not been withdrawn from marketing for any reason from any country. Applications for marketing were not pending elsewhere at the time of this review.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

On May 17, 2001, the FDA confirmed its acceptance that the preclinical sections of the Cipro XR NDA contain only a cross-reference statement to already-approved Cipro® IV, Cipro® Tablets, and Cipro® Oral Suspension NDAs thus confirming that no preclinical information was required for this NDA.

A. Pharmacology and Toxicology:

The applicant did not submit new pharmacology/toxicology data in support of this NDA.

B. Microbiology

Ciprofloxacin inhibits nearly all of the Enterobacterieacae the most common urinary tract pathogens. The applicant did not submit new microbiology data beyond what is reviewed in the clinical trial.

C. Pharmacokinetics and Pharmacodynamics

The ciprofloxacin (b) (4) tablet formulation contains 2 different salts of ciprofloxacin, ciprofloxacin hydrochloride and ciprofloxacin betaine hydrate, and is composed of 2 separate layers. The first layer releases approximately 35% of the dose immediately after intake, and the second has an immediate onset of release with a marginally slower release rate profile, making available the remaining 65% of the dose over the 24-hour dosing interval. Both the immediate-release and controlled-release layers of the tablet are composed of different ratios of ciprofloxacin hydrochloride and ciprofloxacin betaine. The (b) (4) exhibits dissolution characteristics aimed to deliver the equivalent exposure to drug as the corresponding conventional ciprofloxacin tablet (Cipro®) BID treatment (e.g., 500 mg once-daily tablet is equivalent to two 250 mg standard tablets).

The peak concentration (Cmax) of Ciprofloxacin XR given every 24 hours was 35% to 27% higher (Day 1 and Day 5, respectively) than the corresponding immediate-release ciprofloxacin given every 12 hours. Median time to maximum plasma concentration (tmax) for Ciprofloxacin XR was 1.5 hours under fasting conditions, which was comparable to that of immediate-release ciprofloxacin. The elimination half-lives for both formulations were also similar (approximately 5 hours). With regard to urine concentrations, significantly higher ciprofloxacin concentrations were observed after administration of the Ciprofloxacin XR formulation as compared with the corresponding dose of the conventional formulation for the first 12 hours postdose, which may potentially provide improved urine bactericidal activity.

Medical Officer's Comment: *The MO noted the applicant's statements regarding urinary concentrations of Cipro XR. However, the final statement regarding improved bactericidal activity is merely a supposition.*

III. Description of Clinical Data and Sources

A. Overall Data

The materials reviewed included the electronic NDA submitted by the applicant. This consisted primarily of one phase III clinical trial conducted by the applicant. The MO also performed a review of the recent literature.

B. Table Listing the Clinical Trials

The clinical data were derived from one phase III, prospective, active-controlled, randomized, double blind, multicenter study (Study 100346) conducted in the United States in adult female patients (ages 18 to 65 years) with uncomplicated urinary tract infections. 58 of 63 outpatient centers enrolled patients.

Table 2
Pivotal Study 100346

Dates	Design	Treatment/ Dose[a]	Duration of Rx	# Patients Enrolled Per Treatment Arm	Age[b] Range (Mean) years	Race % B/W/O[b,c]
3/7/01 to 10/22/01	Active-Controlled, Randomized, Double-Blind, Multicenter	Cipro XR 500 mg PO QD	3 days	452	18-79 (35.1)	10/78/12
		Cipro® 250 mg PO BID	3 days	453	18-76 (34.7)	8/80/12

a QD = once daily, BID = twice daily
b Randomized population
c B = Black, W = White, O = Other

C. Postmarketing Experience

Worldwide safety information was available for the marketed forms of ciprofloxacin.

IV. Clinical Review Methods

The MO reviewed a random sample of CRFs generated by the FDA statistical reviewer that represented 20% of the patient population. The MO determined that the clinical trial was conducted in accordance with current guidelines and as delineated in the original protocol. Additionally, it was apparent that all data was transcribed accurately and that the trial was conducted ethically. Financial disclosure information was submitted and there appeared to be no issues of conflict of interest. The MO elected to accept the applicant's patient population as well as the results of the clinical trial.

V. Integrated Review of Efficacy

A. Clinical Trial Review

Study 100346:

Title: Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily Modified Release (Cipro XR) 500 mg Tablets QD for 3 Days Versus Conventional Ciprofloxacin 250 mg Tablets BID for 3 Days in the Treatment of Patients With Uncomplicated Urinary Tract Infections

Study Dates: March 7, 2001 to November 26, 2001

Investigators:

(b) (4)

Summary:

This was a multicenter, prospective, randomized, double blind, parallel group, 3-day, Phase III clinical trial conducted at 58 centers in the US (63 centers were recruited but only 58 enrolled patients). Women between the ages of 18 and 65 with an acute uncomplicated UTI (at least 2 of the following symptoms: dysuria, frequency, urgency, suprapubic pain) that could be treated on an outpatient basis were eligible for enrollment. Patients had to have had onset of symptoms for ≤72 hours prior to study entry and a positive pretreatment clean-catch midstream urine culture at enrollment in the study, defined as $\geq 10^5$ CFU/mL as well as pyuria (defined as ≥10 leukocytes/mm^3 in unspun urine examined in a counting chamber) prior to study entry.

Excluded were male subjects, pregnant or nursing patients, patient with asymptomatic bacteriuria or with CUTI and predisposing factors, patients with symptoms of a UTI within the 4 weeks prior to the present episode; patients with onset of symptoms >72 hours or more prior to study entry or with 3 or more episodes of uncomplicated UTI in the past 12 months. Additionally excluded were subjects who received systemic antimicrobial therapy within 48 hours prior to entry,

The primary objective was to determine if Cipro XR 500 mg PO QD for 3 days was non-inferior to conventional ciprofloxacin 250 mg PO BID for 3 days in the treatment of women with uncomplicated UTI. The primary efficacy variable was bacteriological outcome at the TOC (4 to 11 days post-treatment). Secondary objectives were to compare the clinical response rate between treatments at the TOC, and to compare bacteriological and clinical response rates at the late follow-up visit (25 to 50 days post-treatment).

Patients were screened at a pretherapy visit before beginning study drug dosing on Day 1. Patients who consented to participate in the study and met the inclusion and exclusion criteria underwent a physical examination and complete medical history. Serum and urine samples were obtained for a pregnancy test, and blood samples were obtained for CBC/platelets, blood chemistry, and theophylline and prothrombin time tests (only for patients taking theophylline or warfarin, respectively). A clean-catch midstream urine specimen was collected for culture and susceptibility testing and urinalysis. Baseline clinical assessment was performed using a scoring system of clinical signs and symptoms as follows (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe)

After informed consent was obtained, patients were randomly assigned to 1 of the 2 drug treatment groups (Cipro XR 500 mg PO QD for 3 days or Cipro® 250 mg PO BID for 3 days).

At the TOC (4 to 11 days post-treatment) clinical signs and symptoms were assessed and blood and urine samples were collected for laboratory testing, as described for the pretherapy visit including a serum pregnancy test for women of childbearing potential and urine culture and susceptibility testing.

Medical Officer's Comment: *In order to include more data in the analyses, the applicant extended the TOC window from 5 to 9 days post-treatment to 4 to 11 days post-treatment (per protocol amendment 4, dated 20 Dec 2001). The long-term follow-up window was expanded from 28 to 42 days post-treatment to 25 to 50 days post-treatment (per protocol amendment 4, dated 20 Dec 2001). For MO comment see Background section of MOR.*

At the late follow-up visit (25 to 50 days post-treatment), all patients were given a physical examination and were monitored for evidence of any AEs. A clinical assessment was performed based on the same scoring system of the clinical signs and symptoms as used at the TOC. A clean-catch midstream urine culture for organism identification and susceptibility testing also was obtained. Subcultures of all pretreatment causative organisms, organisms persisting at the TOC and at the late follow-up visit, organisms identified during active treatment, or organisms isolated from patients who failed study treatment were also forwarded to a central laboratory for identification and sensitivity testing.

All routine clinical laboratory testing and culture and susceptibility testing were done centrally by (b) (4)

If, following the full 3-day course of therapy, the investigator felt that continued antimicrobial drug therapy was warranted, the patient was to be classified as a treatment failure and prior to the institution of alternative antimicrobial treatment, the patient was evaluated and appropriate laboratory tests, including cultures were performed so that the information to evaluate the study drug would be available. Following the course of alternative antibiotic therapy, the patient underwent a physical examination and a clinical assessment at a post-alternative antibiotic therapy visit (Days 2 to 4 post-treatment) to determine the clinical outcome to alternative antibiotic therapy.

A during-therapy visit (Days 2 to 3) was required of a subset of patients from 10 participating sites. Blood and urine samples were obtained during the course of study drug administration to determine ciprofloxacin concentrations in patients treated in the clinical setting. Safety assessments, including laboratory tests, AE monitoring, and vital signs, were conducted periodically throughout the study drug dosing period and after the end of dosing.

Patients could withdraw consent and be withdrawn from the study at any time. They could also be withdrawn from the study by the investigator or sponsor for an elevated

pre-enrollment laboratory test, AEs, or clinically significant laboratory abnormalities. In addition, patients could be removed from the study if they failed to comply with any aspect of the protocol.

Statistics:

The primary efficacy variable was bacteriological response at the TOC (4 to 11 days post-treatment). Bacteriological response at the late follow-up visit (25 to 50 days post-treatment), and clinical response at the TOC and late follow- up post-treatment visits were considered secondary variables.

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 test-of-cure visit), the following criteria had to be met:

- All inclusion/exclusion criteria were met;
- Study drug was given for a minimum of 2 days (4 doses) if the clinical outcome at the TOC was failure, or a minimum of 3 days (at least 5 doses or 8 tablets) if the clinical outcome at the TOC was cure;
- All bacteriological outcomes were determined at the TOC unless the patient was an early treatment failure (patients with a response of indeterminate at the TOC 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 unless the patient was a treatment failure;
- No protocol violation occurred during the course of therapy influencing treatment efficacy; and
- Study blind was not broken.

An intent-to-treat (ITT) analysis was performed on all patients who received at least 1 dose of study drug. The ITT population also was defined as the population of patients valid for safety. Patients with missing or indeterminate efficacy evaluations were included and counted as nonsuccesses in all efficacy analyses carried out in the ITT population. Patients with missing or indeterminate efficacy evaluations were not included in efficacy analyses carried out in the per-protocol population. All results of the trial were assessed, not only for patients who completed the trial, but also for dropouts with an assessment available after randomization.

The primary efficacy objective of the study was to demonstrate non-inferiority of the Cipro XR group to the Cipro® BID group. To determine whether the Cipro XR group

was non-inferior, a null hypothesis was constructed, which specified that the Cipro® BID group had an eradication rate higher than the Cipro XR group by at least 10%. If this null hypothesis of Cipro® BID superiority could be rejected, the conclusion would be that Cipro XR was non-inferior to Cipro® BID.

Non-inferiority was defined statistically as the lower limit of the 2-sided 95% confidence interval for the difference between treatment groups being greater than –10%.

Definitions of Response:

Bacteriological outcome at the TOC (Day +4 to +11):

Bacteriological outcome at the TOC (4 to 11 days post-treatment) was graded as follows:

- **Eradication**: A urine culture taken within the post therapy window of Days +4 to +11 showed that all uropathogens isolated at study entry in a quantity $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL.

- **Persistence**: A urine culture taken 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 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 completed.

- **Indeterminate**: Patients in whom a bacteriological assessment was not possible to determine. Reasons for indeterminate evaluation must have been documented.

Bacteriological outcome at the late follow-up visit (Day +25 to +50):

Bacteriological outcome at the late follow-up visit (25 to 50 days post-treatment) was graded as follows:

- **Continued Eradication:** Causative organism(s) in quantities $<10^4$ CFU/mL at the test-of-cure and at late follow-up visits.

- **Persistence**: Patients with a causative organism $\geq 10^4$ CFU/mL noted at the test-of-cure visit (+4 to +11 days post-treatment) regardless of the results of the culture at the follow-up visit were to be carried forward.

- **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, with symptoms of infection as previously stated.

- **Recurrence:** Causative organism(s) in numbers < 10^4 CFU/mL at the test-of-cure visit, but reappearance of the same organism(s) ≥ 10^4 CFU/mL before or at the late follow-up visit.

- **New Infection:** A pathogen ≥ 10^5 CFU/mL other than the original microorganism found at baseline was present at a level ≥ 10^5 CFU/mL anytime after treatment was finished.

- **Indeterminate:** Bacteriological outcome to study drug could not be evaluated for any reason (e.g., post-treatment culture not obtainable). The reason must have been recorded in the CRF.

Clinical outcome:

Clinical outcome was based on serial evaluations to determine the effect of therapy on the signs and symptoms (dysuria, frequency, urgency, or suprapubic pain) of the infection. At each evaluation, each of the 4 clinical signs and symptoms were assigned a severity score from 0 (none present) to 3 (severe).

Clinical outcome at the TOC (Day +4 to +11):

Clinical outcome at the TOC (4 to 11 days post-treatment) was graded as follows:

- **Clinical Cure**: Disappearance or improvement of acute signs and symptoms of infection such that alternative antimicrobial therapy was not required or administered.

- **Clinical Failure**: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before the test-of-cure visit, or use of additional antimicrobial therapy for the current infection.

- **Indeterminate**: Patients in whom clinical assessment was not possible to determine. The reason for the indeterminate evaluation must have been documented. Patients graded as indeterminate at this visit were invalid for efficacy evaluation.

Clinical outcome at the late follow-up visit (Day +25 to +50):

Clinical outcome at the late follow-up visit (25 to 50 days post-treatment) for those patients who did not receive alternative antimicrobial therapy at the TOC 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**: Patients carried forward from the test-of-cure visit.

- **Relapse**: Reappearance of signs and symptoms of an uncomplicated UTI considered to be related to an infectious (bacterial) process such that institution of alternative antimicrobial therapy was required.

- **Indeterminate**: Patients in whom clinical assessment was not possible to determine. The reason for indeterminate evaluation must have been documented.

Protocol Amendments:

On 12 April 2001, Bayer submitted a protocol amendment (information on new investigators and statement of transfer of sponsor responsibilities) to 100346. On 12 April 2001, Bayer submitted Amendment 1 (change in protocol) to protocol 100346 (uncomplicated UTI). The purpose of the amendment was to incorporate changes to the protocol due to suggestions from FDA and the investigator meeting.

On 14 May 2001, Bayer submitted Amendment 2 (change in protocol) to protocol 100346 (uncomplicated UTI). The purpose of the amendment was to incorporate changes to the protocol regarding the decreased validity rate (from 80% to 60% validity).

On 31 August 2001, Bayer submitted Amendment 3 (change in protocol) to protocol 100346 (uncomplicated UTI). The purpose of the amendment was to increase the sample size to 820 patients based on a new validity assessment of 50%; redefine the number of valid patients needed for analysis; delete an exclusion criterion; and correct the definition of Recurrence at the late follow-up visit.

On 4 January 2002, Bayer submitted Amendment 4 (change in protocol) to Protocol 100346 (uncomplicated UTI). This amendment was signed off by Bayer on 20 December 2001, before the random code was broken. The purpose of the amendment was to expand the test-of-cure visit window from 5 to 9 days to 4 to 11 days after the last dose of study drug; expand the late follow-up visit window from 28 to 42 days to 25 to 50 days after the last dose of study drug; redefine the administration of concomitant medications in the Exclusion Criteria; clarify the validity criteria; and redefine adverse events.

Patient Disposition and Evaluability/Demographics:

905 patients were enrolled at 58 centers. 452 (50%) were assigned to treatment with Cipro XR and 453 (50%) were assigned to treatment with Cipro® BID. No center enrolled more than 5.8% of subjects or accounted for more than 7.5% of the per protocol population utilized for the primary efficacy analyses.

13/452 (3%) in the Cipro XR group and 11/453 (2%) in the Cipro® BID group prematurely discontinued treatment. The most common reason for discontinuation was lost to follow-up (6 Cipro XR and 7 Cipro® BID), 439 (97%) of the Cipro XR subjects and 442 (98%) of the Cipro® BID subjects completed the study.

Table 3
Reasons for premature discontinuation of treatment

	Cipro XR (N=452)	Cipro® BID (N=453)
Any reason	13 (3%)	11 (2%)
Adverse event	2 (<1%)	2 (<1%)
Patient noncompliance	2 (<1%)	0 (0%)
Consent withdrawn	2 (<1%)	0 (0%)
Insufficient therapeutic effect	1 (<1%)	1 (<1%)
Patient lost to follow-up	6 (1%)	7 (2%)
Protocol violation	0 (0%)	1 (<1%)

8 patients in the Cipro XR group and 7 in the Cipro® BID group did not receive study medication. All 8 from the Cipro XR group and 6 from the BID group were excluded from the safety population. 1 BID patient was included in the safety analysis because she reported an adverse event.

199/452 (44%) of the Cipro XR patients were considered valid for efficacy by the applicant as compared to 223/453 (49%) of the Cipro® BID patients. This difference appeared to be due to the more frequent lack of a causative organism on the Cipro XR arm and was the most common reason for exclusion from the efficacy analysis in both treatment groups.

Table 4
Patient validity

	Cipro XR	Cipro® BID
All patients randomized	452 (100%)	453 (100%)
Valid for safety	444 (98%)	447 (99%)
Valid for efficacy	199 (44%)	223 (49%)

Table 5
By Center Distribution of Patients

	CIPRO XR			CIPRO® BID		
Center	**Randomized**	**ITT**	**Per Protocol**	**Randomized**	**ITT**	**Per Protocol**
1	4	4	1	3	3	3
2	9	9	4	10	9	5
3	20	20	8	21	21	11
4	15	15	4	15	14	8
5	26	25	15	26	26	14
6	24	23	9	24	24	16

7	8	8	5	8	8	5
8	2	2	1	4	4	3
9	10	10	5	10	10	6
10	14	14	7	14	14	7
11	6	6	3	6	6	2
12	23	23	10	23	23	11
13	16	16	7	15	15	7
14	5	5	2	5	5	3
15	15	15	2	14	14	6
16	4	4	2	4	4	2
17	1	1	0	2	2	0
18	8	8	6	8	8	2
19	9	8	3	9	9	7
20	9	9	4	8	8	5
21	8	8	2	7	7	2
22	2	2	1	2	2	0
23	20	19	14	20	20	11
24	11	11	7	10	9	2
25	2	2	1	2	2	1
26	-	-	-	1	1	0
27	7	7	2	8	8	2
28	7	7	3	7	7	3
29	11	11	9	10	10	5
30	10	10	2	9	9	6
31	3	3	2	3	3	0
32	3	3	2	2	2	0
34	5	4	4	6	6	5
35	8	8	2	8	8	4
37	4	4	2	4	3	2
39	10	10	6	10	10	5
40	1	1	0	-	-	-
41	18	18	8	18	18	10
42	4	4	2	5	5	1
44	4	4	1	4	4	2
45	3	3	0	3	3	2
5	5	4	2	5	5	3
47	7	7	2	8	8	1
50	3	3	1	3	3	1
52	14	14	8	13	13	6
55	-	-	-	1	1	0
56	6	6	0	6	6	4
57	8	8	4	7	7	6
58	4	4	2	4	4	1
59	2	2	1	-	-	-
60	3	2	0	4	4	1

61	4	4	2	4	4	1
62	1	1	1	1	1	0
63	5	5	0	5	5	1
64	17	17	6	17	17	11
65	-	-	-	1	1	0
66	-	-	-	1	1	0
67	3	3	2	3	3	1
TOTAL	**452**	**444**	**199**	**453**	**447**	**223**

Protocol deviations

3 patients (2 in the Cipro XR group and 1 in the Cipro® BID group received other antimicrobial agents before the TOC.

Table 6
Reasons for exclusion from efficacy analysis

	Cipro XR (N=452)	**Cipro® BID (N=453)**
Any reason	**253 (56%)**	**230 (52%)**
No causative organism (<10^5 CFU/mL)	221 (49%)	200 (44%)
Noncompliance	1 (0.2%)	1 (0.2%)
Other Antibiotics	2 (0.4%)	1 (0.2%)
Lost to Follow-up	-	1 (0.2%)
No TOC urine culture	15 (3%)	12 (3%)
Inclusion/Exclusion violation	6 (1%)	9 (2%)
Did not receive study drug	8 (2%)	6 (1%)

The inclusion/exclusion criteria violations included the following: age > 65 years; liver function tests > 3 times the upper limit of normal at study entry; more than 2 UTIs in the last 12 months; no evidence of pyuria; and evidence of CUTI.

Because a large number of patients had TOC assessments performed outside the protocol-specified window, the window for the TOC visit was expanded from 5 to 9 days post-treatment to 4 to 11 days (Protocol Amendment 4, dated 20 Dec 2001). This change resulted in the addition of 26 patients to the valid for efficacy population. For similar reasons, the window for the late follow-up visit was expanded from 28 to 42 days post-treatment to 25 to 50 days (Protocol Amendment 4, dated 20 Dec 2001). An additional 30 patients were included in the analysis of the long-term follow-up timepoint as a result of this window expansion.

In addition, it was discovered that 1 patient (Patient 52027) enrolled in the study was a man undergoing a sex-change operation. This patient was deemed to be invalid for efficacy since only women were to be enrolled.

Medical Officer's Comment: *The number of patients excluded from the valid for efficacy population due to the lack of a causative organism is typical of trials for this indication.*

Exclusions for other reasons were relatively few and again numerically consistent with those seen in other trials.

.Demographics:

The distribution of demographic variables in the Cipro XR and Cipro® BID groups was similar. The population was primarily Caucasian, with symptoms of 2 – 3 days duration.

Table 7
Demographics
Valid for Efficacy Population

	Cipro XR (N=199)	Cipro® BID (N=223)
Lactating, % No	100%	100%
Adequate birth control, % Yes	100%	100%
Race, % Caucasian	77%	80%
Health status, % Excellent	59%	59%
Age at enrollment (yr), Mean	34.3	35.1
Weight at enrollment (kg), Mean	70.5	70.5
Duration of infection (days)		
1	11%	17%
2	46%	43%
3	38%	35%
4[a]	5%	4%
Number of UTI episodes last year		
0	67%	70%
1	26%	23%
2	8%	8%

UTI = urinary traction infection
[a]≤72 hours

Medical Officer's Comment: *The 2 treatment groups appeared well balanced with respect to the distribution of symptoms and symptom severity. Overall, frequency was the most common symptom (98%), and suprapubic pain was the least common (76%). The symptom of urgency was severe in 37% of patients overall, the highest proportion of patients in the severe category for any of the 4 signs or symptoms.*

199 Cipro XR subjects had a causative organism as compared to 223 Cipro® BID subjects.

The demographic data, signs and symptoms at entry, and pretherapy causative organisms for the valid for safety population were consistent with the results for the valid for efficacy population. 469 patients (53%) valid for safety had at least 1 causative organism.

Treatment compliance

Only 2 valid for efficacy patients failed to take all 9 tablets; both of these patients took a total of 8 tablets. All valid for efficacy patients received treatment over the course of 3 or 4 days, depending on when the first of the 2 daily doses was taken (morning or afternoon); in either case, the duration of the study drug treatment period was 72 hours. (mean 3 days, median 3 days)

Previous and Concomitant medication;

None of the valid for efficacy subjects received previous antimicrobials. 4/444 Cipro XR and 4/447 Cipro® BID subjects received previous antimicrobials including levofloxacin, Flagyl, TMP and TMP/SMX.

5 Cipro XR subjects and 3 Cipro® BID subjects received concomitant antimicrobials. TMP/SMX in 3 patients, and ciprofloxacin, levofloxacin, metronidazole, ceftriaxone, and TMP alone in 1 patient each.

Efficacy results

Primary Efficacy Parameter:
(Bacteriological response at the TOC (4 to 11 days post-treatment).

Table 8
Bacteriological response at TOC (4 to 11 days post-treatment)
Valid for Efficacy Population

	Cipro (b) (4) (N = 199)	Cipro® BID (N=223)	FDA 95% CI (with CCF*)
Eradication	188 (94.5%)	209 (93.7%)	- 4.2%, 5.7%
Persistence	8 (4.0%)	11 (4.9%)	
New infection	3 (1.5%)	3 (1.3%)	

* = continuity correction factor

***Medical Officer's Comment:**, The applicant met the stated objective of non inferiority between the Cipro XR and the Cipro® BID formulations within the pre-specified in the protocol delta of ± 10 with a lower limit of the CI of – 4.2%.*

A by center efficacy analysis revealed similar eradication rates across the centers with 16 centers having 100% eradication rates in both treatment groups. 7 centers had higher eradication rates in the Cipro XR group and 7 had higher eradication rates in the Cipro® BID group. The 2 pools of small centers combined had eradication rates of 100% in the Cipro (b) (4) group and 91% in the Cipro® BID group.

Table 9
By Center Eradication Rates at the TOC
Valid for Efficacy Population

Center	Cipro XR N/N	Cipro® BID N/N
2	4/4 (100%)	5/5 (100%)
3	8/8 (100%)	11/11 (100%)
4	3/4 (75%)	8/8 (100%)
5	15/15 (100%)	14/14 (100%)
6	9/9 (100%)	13/16 (81%)
7	5/5 (100%)	5/5 (100%)
9	5/5 (100%)	6/6 (100%)
10	6/7 (86%)	7/7 (100%)
12	10/10 (100%)	11/11 (100%)
13	7/7 (100%)	6/7 (86%)
14	2/2 (100%)	3/3 (100%)
15	2/2 (100%)	6/6 (100%)
18	6/6 (100%)	2/2 (100%)
19	3/3 (100%)	7/7 (100%)
20	4/4 (100%)	5/5 (100%)
23	13/14 (93%)	11/11 (100%)
24	7/7 (100%)	2/2 (100%)
28	3/3 (100%)	3/3 (100%)
29	7/9 (78%)	5/5 (100%)
30	2/2 (100%)	6/6 (100%)
34	4/4 (100%)	4/5 (80%)
35	2/2 (100%)	4/4 (100%)
39	3/6 (50%)	4/5 (80%)
41	7/8 (88%)	7/10 (70%)
46	2/2 (100%)	3/3 (100%)
52	7/8 (88%)	6/6 (100%)
57	3/4 (75%)	5/6 (83%)
64	6/6 (100%)	10/11 (91%)
200	13/13 (100%)	13/15 (87%)
300	20/20 (100%)	17/18 (94%)

* Center 200 = pool of centers 8, 16, 22, 32, 42, 44, 50, 56, 58, 60, 62
* Center 300 = pool of centers 1, 11, 21, 25, 27, 31, 37, 45, 47, 59, 61, 63, 67

Bacteriologic response by causative organism can be seen below:

Table 10
Microbiologic Outcome of Original Causative Organism at the TOC
Valid for Efficacy Population

	Cipro XR N = 199 (204 Original Organisms)	**Cipro® BID N = 223 (239 Original Organisms)**
	Eradication N (%)	**Eradication N (%)**
Escherichia coli	156/160 (97.5%)	176/181 (97%)
Enterococcus faecalis	10/11 (91%)	17/21 (81%)
Klebsiella pneumoniae	7/9 (78%)	11/14 (79%)
Proteus mirabilis	11/12 (92%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83%)	7/7 (100%)
Enterobacter aerogenes	2/2 (100%)	3/3 (100%)
Enterobacter cloacae	2/2 (100%)	2/2 (100%)
Citrobacter koseri	-	2/2 (100%)
Klebsiella ornithinolytica	-	2/2 (100%)
Proteus vulgaris	1/1 (100%)	-
Stenotrophomonas maltophilia	1/1 (100%)	-

Medical Officer's Comment: *There were similar bacteriologic response rates versus Escherichia coli, and Klebsiella pneumoniae. Cipro XR was numerically superior versus Enterococcus faecalis and Cipro® BID was numerically superior versus Staphylococcus saprophyticus and Proteus mirabilis.*

A new infecting organism was identified in 3 Cipro XR subjects and 4 Cipro® BID subjects. In all 7, the organism causing new infection was identified as Enterococcus. faecalis.

Bacteriologic response at the late follow up visit was also within the prespecified delta of ±10 with a lower limit of the CI of – 6.9%, thus indicating non inferiority of Cipro XR to Cipro® BID at the later visit.

Table 11
Bacteriological response at late follow-up (25 to 50 days post-treatment)
Valid for Efficacy Population

	Cipro XR (N=199)	Cipro® BID (N=223)	FDA 95% CI (with CCF*)
Continued eradication	151 (75.9%)	165 (74%)	- 6.86%, 9.69%
Eradication with recurrence	14 (7%)	17 (7.6%)	
Persistence	8 (4%)	11 (4.9%)	
New infection	3 (1.5%)	10 (4.5%)	
Indeterminate	23 (11.6%)	20 (9%)	

* = continuity correction factor

The slightly higher rate of continued eradication in the Cipro XR group appeared to be due to a difference in new infection rates between treatments. The Cipro® BID group had 10 new infections, 7 of which occurred between the TOC and late follow-up visits whereas the Cipro XR group had 3 new infections, all of which had occurred by the TOC.

Table 12
Bacteriological eradication rates by organism
late follow-up (25 to 50 days post-treatment)
Valid for Efficacy Population

	Cipro XR	Cipro® BID
	Eradication N (%)	**Eradication N (%)**
Escherichia coli	124/160 (78%)	150/181 (83%)
Enterococcus faecalis	9/11 (82%)	11/21 (52%)
Klebsiella pneumoniae	3/9 (33%)	6/14 (50%)
Proteus mirabilis	10/12 (83%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83%)	6/7 (86%)
Enterobacter aerogenes	1/2 (50%)	3/3 (100%)
Enterobacter cloacae	2/2 (100%)	2/2 (100%)
Citrobacter koseri	-	1/2 (50%)
Klebsiella ornithinolytica	-	2/2 (100%)
Proteus vulgaris	1 (100%)	-
Stenotrophomonas maltophilia	1 (100%)	-

* **bold** type denotes requested pathogens

The continued eradication rates at late follow-up were higher on the Cipro® BID arm for *Escherichia coli, Proteus mirabilis*, *Klebsiella pneumoniae,* and *Staphylococcus saprophyticus*.

In addition to the 7 new infections identified at the TOC, there were 11 more identified at late follow up, 8 on the Cipro® BID arm and 3 on the Cipro XR arm. 2 Cipro XR subjects and 5 Cipro® BID subjects had new infections due to *Enterococcus faecalis* (total 5 and 9 respectively). The remaining Cipro XR subject had a new infection due to *Klebsiella pneumoniae* and there were 3 new infections due to *Escherichia coli* on the Cipro® BID arm.

Clinical response:

Table 13
Clinical response at TOC (4 to 11 days post-treatment)
Valid for Efficacy Population

Clinical Cure	Cipro XR	Cipro® BID	FDA 95% CI (with CCF*)
TOC (Day +4 to +11)	189/198 (95.5%)	204/220 (92.7%)	- 2.2%, 7.7%
Late Follow-Up (Day +25 to +50)	161/181 (89%)	187/216 (86.6%)	- 4.6%, 9.3%

* = continuity correction factor

Medical Officer's Comment: *The results for clinical response were consistent with the results for bacteriological response. The Cipro XR group had a slightly higher clinical success rate than did the Cipro® BID group (95.5% and 92.7%, respectively). Because the lower limit of the 95% confidence interval for the treatment group difference (-2.2%) was higher than –10%, Cipro XR was shown to be non-inferior to Cipro® BID at both timepoints.*

There were 11 relapses on the Cipro XR arm (5.5%) and 13 (5.8%) on the Cipro® BID arm.

As noted in the introduction in addition to establishing non-inferiority, the applicant is requested to show correlation between clinical and bacteriological response. In this study, there was correlation between outcomes in 93% of subjects (either both successful outcomes or both unsuccessful outcomes). 15 patients with a bacteriological response of eradication had a clinical response of failure (5 Cipro XR, 10 Cipro® BID), 10 patients with a bacteriological response of persistence had a clinical response of cure (5 each arm), and 5 of 6 patients who developed new bacteriological infections had a clinical response of cure (2 Cipro XR, 3 Cipro® BID).

Post therapy antimicrobial agents were used by 25 (13%) Cipro XR patients and 28 (13%) Cipro® BID patients. Ciprofloxacin and levofloxacin were the most commonly used post therapy antimicrobial agents. Other antimicrobials used that are not considered to have coverage against uropathogens included: PCN VK, metronidazole, erythromycin, clarithromycin and azithromycin. One patient was given PCN VK for a recurrent UTI and in that case only, PCN VK was considered to have coverage since it was given by the investigator. All of the above subjects were included in the valid for efficacy population and were classified as failures or relapses.

Valid for Safety Population:

Medical Officer's Comment: *The bacteriological results for the valid for safety population were consistent with the bacteriological results for the valid for efficacy population at the TOC and late follow-up visits, and the Cipro XR group was shown to be*

non-inferior to the Cipro® BID group at the TOC and marginally so at the late follow up visit.

Table 14
Microbiologic and Clinical Outcome
Valid for Safety Population

	Cipro XR	Cipro® BID	FDA 95% CI (with CCF*)
Microbiologic Eradication			
TOC (Day +4 to +11)	193/223 (86.5%)	215/248 (87.4%)	- 6.7%. 6.4%
Late Follow-Up (Day +25 to +50)	159/223 (71.3%)	175/248 (71.1%)	- 7.9% , 9.4%
Clinical Cure			
TOC (Day +4 to +11)	382/444 (86%)	395/447 (88.4%)	- 6.9%, 2.3%
Late Follow-Up (Day +25 to +50)	335/444 (75.5%)	357/447 (79.9%)	- 10.1%, 1.3%

* = continuity correction factor

The main difference between the valid for safety population and the valid for efficacy population was the clinical response at the TOC visit for patients with no pretherapy organisms. For this group of patients, the failure rate was 12.2% for the Cipro XR group compared with 4.5% for the Cipro® BID group (27 and 9).

There was a similar difference between treatment groups in the clinical response rates at the late follow-up visit (25 to 50 days post-treatment) in the valid for safety population. Due to a higher rate of failures and relapses, as well as a higher rate of patients with missing and indeterminate responses, the Cipro XR group had a 75.5% success rate at late follow-up compared with 79.9% in the Cipro® BID group. The 95% CI for this timepoint was (–10.1%, 0.9%) indicating only borderline non-inferiority.

MO comments on Bacteriologic Efficacy:

The applicant's submission contained adequate data to allow for an approval for the use of Cipro XR in the treatment of uncomplicated UTI caused by Escherichia coli, Enterococcus faecalis, and Proteus mirabilis. There was inadequate data to support an approval for Klebsiella pneumoniae.

Although Staphylococcus saprophyticus is the second most common pathogen causing acute cystitis after Escherichia coli (5% to 15%), there were too few isolates (6) to support an approval. The MO requested that the applicant submit additional data regarding isolates found that met the following criteria: "Patients had to have had onset of symptoms for ≤72 hours prior to study entry and a positive pretreatment clean-catch midstream urine culture at enrollment in the study, defined as ≥10^4 CFU/mL as well as pyuria (defined as ≥10 leukocytes/mm^3 in un-spun urine examined in a counting chamber) prior to study entry".

The rationale for this request can be found in the literature that supports the designation of isolates of Staphylococcus saprophyticus found in quantities of ≥10^4 CFU/mL as pathogens in the presence of symptoms and pyuria.

In response the applicant provided information on only 3 additional patients with Staphylococcus saprophyticus colony counts between 10,000 and 100,000 who would have met the criteria for validity at the TOC if the colony counts had been 100,000. Only 1 of these patients received Cipro XR and was a clinical cure with eradication at the TOC as compared to 2 Cipro® BID patients with similar outcomes.

Table 15

Patients with *Staphylococcus saprophyticus* at >10^4 and <10^5Pre-Therapy

	Cipro XR	Cipro® BID
Bacteriological Response at TOC	1 Eradication	2 Eradications
Bacteriological Response at F/u	1 Indeterminate*	2 Continued Eradications
Clinical Response at TOC	1 Cure	2 Cures
Clinical Response at F/u	1 Missing*	2 Continued Cures

* The CIPRO XR patient with *S. saprophyticus* had her follow-up response visit just outside (before) the follow-up window. The follow-up window was 25-50 days after EOT, and the patient had her evaluation on day +24. The patient had a *negative culture* and was called a *continued cure*, but because the visit was not in the window, these responses are coded as indeterminate/missing.

Thus there were 13 valid patients with *Staphylococcus saprophyticus* at 10^5 colony count; 6 Cipro XR, 7 Cipro® BID as well as 1 additional Cipro XR and 2 additional Cipro® BID subjects with counts **>10^4** for a total of 7 Cipro XR and 9 Cipro® BID subjects. As noted above for [redacted] (b) (4) the amount of data provided was inadequate to support an approval versus *Staphylococcus saprophyticus*.

B. Efficacy Conclusions

Cipro XR 500 mg PO QD x 3 days was evaluated against ciprofloxacin 250 mg PO BID for 3 days for the treatment of uncomplicated urinary tract infections in a randomized, double-blind, active-controlled, multicenter phase III study.

905 women were enrolled and 891 (444 in the Cipro XR group and 447 in the Cipro® BID group) received at least one dose of study drug and were included in the valid for safety population. 422 patients (199 in the Cipro XR group and 223 in the Cipro® BID group) fulfilled the criteria for the valid for efficacy population. The treatment groups were similar with respect to baseline demographic variables and infection characteristics. The primary efficacy variable was microbiologic outcome at the TOC. Secondary efficacy variables included clinical response at the TOC, as well as microbiologic and clinical outcomes at the late follow-up visit. Analyses were performed on the valid for efficacy and valid for safety patient populations.

Cipro XR for 3 days was non-inferior to Cipro® BID for 3 days with respect to the primary and secondary efficacy parameters.

Table 16
Microbiologic and Clinical Outcome
Valid for Efficacy Population

	Ciprofloxacin XR 500 mg PO QD x 3 days	Ciprofloxacin 250 mg PO BID x 3 days	FDA 95% CI (with CCF*)
Microbiologic Eradication			
TOC (Day +4 to +11)	188/199 (94.5%)	209/223 (93.7%)	- 4.2%. 5.7%
Late Follow-Up (Day +25 to +50)	151/199 (75.9%)	165/223 (74%)	- 6.9%. 10.6%
Clinical Cure			
TOC (Day +4 to +11)	189/198 (95.5%)	204/220 (92.7%)	- 2.2%, 7.7%
Late Follow-Up (Day +25 to +50)	161/181 (89%)	187/216 (86.6%)	- 4.6%, 9.3%

* = continuity correction factor

Cipro XR was effective against infections caused by the predominant group of pathogens causing uncomplicated urinary tract infections.

Table 17
Microbiologic Outcome of Original Causative Organism at the TOC
Valid for Efficacy Population

	Cipro XR N = 199 (204 Original Organisms)	Cipro® BID N = 223 (239 Original Organisms)
	Eradication N (%)	**Eradication N (%)**
Escherichia coli	156/160 (97.5%)	176/181 (97%)
Enterococcus faecalis	10/11 (91%)	17/21 (81%)
Klebsiella pneumoniae	7/9 (78%)	11/14 (79%)
Proteus mirabilis	11/12 (92%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83%)	7/7 (100%)
Enterobacter aerogenes	2/2 (100%)	3/3 (100%)
Enterobacter cloacae	2/2 (100%)	2/2 (100%)
Citrobacter koseri	-	2/2 (100%)
Klebsiella ornithinolytica	-	2/2 (100%)
Proteus vulgaris	1/1 (100%)	-
Stenotrophomonas maltophilia	1/1 (100%)	-

* **bold** type denotes requested pathogens

In conclusion, Cipro XR at a dose of 500 mg PO once daily for 3 days is effective in the treatment of uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*, *Proteus mirabilis*, and *Enterococcus faecalis*.

VI. Integrated Review of Safety:

The ISS included data from:

- Study 100346: pivotal clinical trial that was conducted in the United States in 905 adult female patients with uncomplicated UTI to evaluate the safety and efficacy of Cipro XR 500 mg tablets versus Cipro® BID for 3 days.

- Studies 10169, 10321, 10322, 10324, 10325, 10339, 10602, and 10603: Phase I, clinical pharmacology studies conducted in Germany to determine the PK of both Cipro XR 500 mg and Cipro XR 1000 mg tablets, and to quantify possible drug-drug interactions with this formulation of ciprofloxacin. Interactions related to the absorption of Cipro XR induced by changes in gastric pH (omeprazole) and by adsorption/chelation (magnesium/aluminum-containing antacid) were studied. A total of 138 volunteers were enrolled in these studies. They were all male Caucasians, ranging in age from 19 to 53 years.

Table 18
Clinical Pharmacology Studies – Germany

Study Number	Number of Subjects	Design	Formulation (Batch No.)	Dose	Duration
Single Dose					
Study 10169	12	3-Way Cross-Over, Randomized (b) (4) vs. IR)	500 mg (b) (4) 500 mg (b) (4) 250 mg IR	500 mg Fasted 500 mg Fed 500 mg Fasted	Once Once Once
Study 10321	20	2-Way Cross-Over, Randomized, Unblinded, Food Effect	1000 mg (b) (4) 1000 mg (b) (4)	1000 mg Fasted 1000 mg Fed (High-Fat, High-Calorie)	Once Once
Study 10322	20	2-Way Cross-Over, Randomized, Unblinded, Food Effect	500 mg (b) (4) 500 mg (b) (4)	500 mg Fasted 500 mg Fed (High-Fat, High-Calorie)	Once Once
Study 10339	12	3-Way Cross-Over, Randomized, Unblinded (b) (4) vs. IR)	1000 mg (b) (4) 1000 mg (b) (4) 500 mg IR	1000 mg Fasted 1000 mg Fed 1000 mg Fasted	Once Once Once
Multiple Dose					
Study 10324	19	Cross-Over, Randomized, Unblinded (b) (4) vs. IR)	1000 mg (b) (4) 500 mg IR	1000 mg QD 500 mg BID	5 days 5 days
Study 10325	19	Cross-Over, Randomized, Unblinded (b) (4) vs. IR)	500 mg (b) (4) 250 mg IR	500 mg QD 250 mg BID	5 days 5 days
Special Studies					
Study 10602	18	4-Way Cross-Over, Randomized, Unblinded	1000 mg (b) (4)	1000 mg Alone 1000 mg 2 hours After Antacid 1000 mg 4 hours Before Antacid	Once Once Once
Study 10603	18	Cross-Over, Randomized, Unblinded	1000 mg (b) (4)	1000 mg Alone 1000 mg 3 days After Omeprazole	Once Once

- Study 100275: an ongoing clinical trial being conducted in the United States and Canada in adult patients with CUTI or acute, uncomplicated pyelonephritis, to evaluate the safety and efficacy of Cipro XR 1000 mg QD versus Cipro® BID for 7 to 14 days. Data on the safety of patients enrolled by 30 November 2001 are included.

Table 20
Ongoing Clinical Trial (Study 100275) – United States and Canada

Start Date	Study Design	Treatment/ Dose[a]	Duration of Treatment
15 April 2001	Active-Controlled, Randomized, Double-Blind, Multicenter (Phase III)	Cipro XR 1000 mg PO QD	7-14 days
		Cipro® 500 mg PO BID	7-14 days

- All sources, domestic and foreign, on conventional, immediate-release ciprofloxacin.

A. Brief Statement of Conclusions

Cipro XR 500 mg PO, QD for 3 days was compared to Cipro® 250 mg PO, BID for 3 days in one adequate and well-controlled pivotal study in uncomplicated UTI. 905 patients enrolled in the study and 444 received at least one dose of Cipro XR and were evaluable for safety. Approximately 98% of all patients received their full dose of study drug over a 72-hour period

The majority of patients in the study were white (79%). Patients of other ethnic origins were represented (9% Black, 9% Hispanic, 2% Asian). The mean age of all patients was 35 years, with a range of 18 to 79 years.

The incidence of AEs in patients treated with Cipro XR was 27%. The body as a whole was the body system with the highest percentage (11%) of AEs. Most (93.5%) AEs were mild to moderate in intensity. No single AE was considered severe in more than 2 patients. Adverse events occurring in at least 2% of patients treated with Cipro XR were headache (4%) and nausea (4%).

Drug-related AEs were reported in 10% of patients, with nausea (3%) and headache (2%) being the only two drug-related AEs occurring in 1% or more of patients. Only 1 (flatulence) of 45 drug-related AEs in the Cipro XR group remained unchanged. All other drug-related AEs either resolved (44) or improved (1).

No patient deaths occurred during the study. Two patients (<1%) were withdrawn early due to an AE and 6 patients (1%) experienced SAEs. The incidence of laboratory test abnormalities, especially clinically significant abnormalities, was low. Descriptive statistics of changes in laboratory test results from baseline did not show any trend that appeared to be uniquely associated with Cipro XR.

Cipro XR and Cipro®BID, both given for 3 days for the treatment of uncomplicated UTI, exhibited similar safety profiles. No clinically meaningful differences were found between the two formulations of ciprofloxacin.

Based on the safety profile of Cipro XR from the pivotal study, the additional safety information available from clinical pharmacology studies, and the long-term clinical experience with ciprofloxacin it is concluded that Cipro in (b) (4) given as 500 mg every 24 hours for 3 days is safe for use for the treatment of uncomplicated urinary tract infections (acute cystitis).

B. Description of Patient Exposure

452 patients were randomized to Cipro XR. Of these, 444 (98%) patients received at least one dose of Cipro XR and were evaluable for safety. The remaining 8 patients did not receive any study drug and were excluded from the safety analysis. 453 patients were randomized to Cipro® BID. Of these 453 patients, 6 did not receive study drug. Thus, there were 447 (99%) patients evaluable for safety in the Cipro®BID group.

437/ 444 patients (98%) who were evaluable for safety in the Cipro XR group and 441/447 patients (99%) who were evaluable for safety in the Cipro®BID group received a total of 9 tablets of study drug. At least 98% of the patients who completed their study drug in both groups took their medication over a period of 72 hours as specified in the protocol. 7 (2%) patients in the Cipro XR group and 5 (1%) patients in the Cipro®BID group received at least one dose of study drug, but less than 9 tablets. It could not be confirmed whether one patient in the Cipro®BID group received any study medication but was included in the population of patients valid for safety, because she reported an AE.

Table 21
Extent of Exposure
Valid for Safety Population

Duration of Treatment (days)[a]

	Data Missing N (%)	≤ 2 N (%)	3 N (%)	4[b] N (%)	≥ 5[c] N (%)
Cipro XR		3 (<1%)	227 (51%)	211 (48%)	3 (1%)
Cipro®BID	1 (<1%)	3 (<1%)	238 (53%)	202 (45%)	3 (1%)

Number of Tablets

	Data Missing N (%)	≤ 6 N (%)	8 N (%)	9[d] N (%)
Cipro XR		3 (<1%)	4 (<1%)	437 (98%)
Cipro®BID	1 (<1%)	3 (<1%)	2 (<1%)	441 (99%)

a Duration of treatment was calculated as the date of last dose of study drug minus the date of the first dose of study drug plus one (without accounting for the time of intake during the day).
b Total duration of 72 hours
c Total number of tablets taken did not exceed the full dose of study drug (9 tablets).
d Full dose of study drug (active and placebo tablets)

C. Study 100346:

Demographics:

All of the patients were female (with the exception of one man who was undergoing a sex-change operation). The majority of patients in the study were white (79%). Patients of other ethnic origins were represented (9% Black, 9% Hispanic, 2% Asian). The mean age of all patients was 35.0 years, with a range of 18 to 79 years.

5/444 (1%) valid for safety patients who were treated with Cipro XR were above 65 years of age. The distribution of age, race, and weight was comparable between the two treatment groups.

Table 22
Demographic Data
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Age (years)		
Mean	35.2	34.8
Standard Deviation	12.6	12.6
Median	33.0	33.0
Range	18-79	18-76
Race (%)		
White	79	80
Black	10	8
Hispanic	9	9
Asian	2	3
American Indian	<1	<1
Missing	<1	
Weight (kg)		
Mean	71.1	70.8
Standard Deviation	19.4	17.0
Median	65.9	67.5
Range	39.5-159.5	41.4-145.0

Adverse Events:

Table 23
Summary of Adverse Events
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Any AE	121 (27%)	105 (23%)
Any Drug-Related AE	46 (10%)	41 (9%)
Any Serious AE	6 (1%)	6 (1%)
Discontinuation Due to an AE	2 (<1%)	2 (<1%)

There were more patients who experienced at least one AE and/or a drug related AE in the Cipro XR group (27%) compared with the Cipro®BID group (23%); rates of SAEs, and premature discontinuations due to AEs were similar in both treatment groups.

All Adverse Events

121/444 (27%) of patients treated with Cipro XR and 105/447 (23%) of patients treated with Cipro®BID reported at least one AE during the course of the study.

The body system with the highest percentage of AEs regardless of relationship to study drug was the body as a whole for both the Cipro XR and Cipro®BID groups (11% vs. 9%). AEs occurring in 2% or more of patients in either the Cipro XR or the control group in this system were headache (4% vs. 3%) and abdominal pain (1% vs. 2%).

The incidence of digestive system AEs was higher in the Cipro XR group (9% vs. 3%). Nausea was the most common event in this system, occurring in 4% of patients treated with Cipro XR and 2% of patients treated with Cipro®BID. The incidence of all other AEs in any body system was comparable between the two groups.

Table 24
AEs By Body System
Valid for Safety Population

	Cipro XR N = 444	**Cipro®BID N = 447**
Any adverse event	121 (27%)	105 (23%)
Body as a Whole		
Any event	51 (11%)	40 (9%)
Headache	16 (4%)	15 (3%)
Abdominal Pain	6 (1%)	7 (2%)
Back Pain	6 (1%)	5 (1%)
Infection Bacterial	6 (1%)	1 (< 1%)
Allergic Reaction	4 (< 1%)	-
Moniliasis	4 (< 1%)	2 (< 1%)
Accidental Injury	3 (< 1%)	2 (< 1%)
Asthenia	3 (< 1%)	6 (1%)
Cyst	2 (< 1%)	-
Chest Pain	2 (< 1%)	1 (< 1%)
Flank Pain	1 (< 1%)	-
Photosensitivity Reaction	1 (< 1%)	-
Facial edema	1 (< 1%)	-
Leg Pan	1 (< 1%)	1 (< 1%)
Neck Rigidity	1 (< 1%)	-
Chills	-	1 (< 1%)
Fever	-	1 (< 1%)
Infection	-	1 (< 1%)
Infection viral	-	1 (< 1%)
Pain	-	2 (< 1%)
Arm Pain	-	1 (< 1%)
Cardiovascular		
Any Event	5 (1%)	6 (1%)
Cardiovascular Disorder	1 (< 1%)	-
Hypertension	1 (< 1%)	1 (< 1%)
Migraine	1 (< 1%)	1 (< 1%)
Peripheral Edema	1 (< 1%)	-
Syncope	1 (< 1%)	-
Cardiomyopathy	-	1 (< 1%)

Table 24
AEs By Body System
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Palpitation	-	1 (< 1%)
Hemorraghe	-	1 (< 1%)
Vasodilatation	-	1 (< 1%)
Digestive		
Any event	40 (9%)	15 (3%)
Nausea	17 (4%)	7 (2%)
Diarrhea	5 (1%)	3 (< 1%)
Vomiting	5 (1%)	1 (< 1%)
Constipation	4 (< 1%)	3 (< 1%)
Dyspepsia	4 (< 1%)	-
Tooth Pain	2 (< 1%)	-
Flatulence	2 (< 1%)	-
Apthous Stomatitis	1 (< 1%)	-
Dry Mouth	1 (< 1%)	-
Mouth Ulceration	1 (< 1%)	-
Oral Moniliasis	1 (< 1%)	-
Colitis	1 (< 1%)	-
Intestinal Obstruction	1 (< 1%)	-
Anorexia	1 (< 1%)	1 (< 1%)
Gastroenteritis	1 (< 1%)	-
Thirst	1 (< 1%)	-
GI disorder	-	2 (< 1%)
GGT Increased	-	1 (< 1%)
Heme and Lymphatic		
Any event	2 (< 1%)	3 (< 1%)
Ecchymoses	1 (< 1%)	-
Lymphadenopathy	1 (< 1%)	-
Anemia	-	3 (< 1%)
Hypochromic anemia	-	1 (< 1%)
Metabolic and Nutritional		
Any event	1 (< 1%)	3 (< 1%)
Hyperglycemia	1 (< 1%)	3 (< 1%)
Musculoskeletal		
Any event	1 (< 1%)	2 (< 1%)
Arthralgia	1 (< 1%)	1 (< 1%)
Myalgia	-	1 (< 1%)
Nervous		
Any event	14 (3%)	10 (2%)
Dizziness	6 (1%)	4 (< 1%)
Somnolence	3 (< 1%)	2 (< 1%)
Insomnia	2 (< 1%)	1 (< 1%)

Table 24
AEs By Body System
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Depersonalization	1 (< 1%)	-
Hypertonia	1 (< 1%)	1 (< 1%)
Incoordination	1 (< 1%)	-
Tremor	1 (< 1%)	-
Vertigo	1 (< 1%)	1 (< 1%)
Anxiety	-	1 (< 1%)
Nervousness	-	1 (< 1%)
Respiratory		
Any event	14 (3%)	16 (4%)
Pharyngitis	8 (2%)	9 (2%)
Increased Cough	3 (< 1%)	1 (< 1%)
Rhinitis	3 (< 1%)	4 (< 1%)
Sinusitis	2 (< 1%)	3 (< 1%)
Bronchitis	-	1 (< 1%)
Epistaxis	-	1 (< 1%)
Skin and appendages		
Any event	10 (2%)	7 (2%)
Rash	3 (< 1%)	4 (< 1%)
Pruritus	3 (< 1%)	-
Acne	1 (< 1%)	1 (< 1%)
Contact dermatitis	1 (< 1%)	-
Maculopapular Rash	1 (< 1%)	-
Vesicolobullous Rash	1 (< 1%)	-
Skin Disorder	1 (< 1%)	-
Sweating	1 (< 1%)	-
Herpes Simplex	-	1 (< 1%)
Alopecia	-	1 (< 1%)
Special Senses		
Any event	3 (< 1%)	1 (< 1%)
Ear disorder	1 (< 1%)	-
Otitis Media	1 (< 1%)	-
Scleritis	1 (< 1%)	-
Taste Perversion	1 (< 1%)	1 (< 1%)
Urogenital		
Any Event	26 (6%)	32 (7%)
Vaginitis	11 (2%)	9 (2%)
Vaginal Moniliasis	5 (1%)	11 (2%)
Pregnancy	3 (< 1%)	4 (< 1%)
Dysmenorrhea	2 (< 1%)	-
Dysuria	2 (< 1%)	-
Abortion	1 (< 1%)	2 (< 1%)

Table 24
AEs By Body System
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Mastitis	1 (< 1%)	-
Menorraghia	1 (< 1%)	-
Metrorraghia	1 (< 1%)	2 (< 1%)
Vaginal Hemorraghe	1 (< 1%)	1 (< 1%)
Kidney calculus	1 (< 1%)	-
Urinary Incontinence	1 (< 1%)	-
Breast Pain	-	1 (< 1%)
Leukorrhea	-	3 (< 1%)
Uterine Disorder	-	1 (< 1%)
Nocturia	-	1 (< 1%)
Pyelonephritis	-	1 (< 1%)
Urine Abnormality	-	1 (< 1%)
Urogenital disorder	-	1 (< 1%)

Severe AEs:

Most events were of mild to moderate severity with more reports of severe AEs on the Cipro®BID arm. 12/444 (3%) of Cipro XR and 15/447 (3%) of Cipro®BID subjects reported severe AEs.

The severe AEs on the Cipro XR arm included 2 reports each of headache and pregnancy, 1 report each of asthenia, bacterial infection, accidental injury, nausea, tooth pain, intestinal obstruction, somnolence, kidney stone, and tremor.

The severe AEs on the Cipro®BID arm included 5 reports of headache, 2 reports each of back pain, pregnancy, and nausea, 1 report each of bacterial infection, cardiomyopathy, diarrhea, constipation, pharyngitis, sinusitis, vaginitis, moniliasis, and abortion.

Table 25
Adverse Events by Severity
Valid for Safety Population

	Cipro XR N = 444		Cipro®BID N = 447	
	All Patients with Events N (%)	All Events[a] N (%)	All Patients with Events N (%)	All Events[a] N (%)
Mild	51 (11)	101 (50.5)	43 (10)	76 (45.8)
Moderate	58 (13)	86 (43)	47 (11)	70 (42.2)
Severe	12 (3)	13 (6.5)	15 (3)	20 (12)
Total		200 (100)		166 (100)

Discontinuations:

8/200 (4%) of AEs in the Cipro XR group and 2/166 (1%) of AEs in the Cipro® BID group resulted in discontinuation of study drug. The events that led to discontinuation occurred in 2 (<1%) patients for each of the two treatment groups (1 Cipro XR subject developed abdominal pain, back pain, nausea, vomiting and dysuria, the other developed a maculopapular rash, pruritus and excoriations, 1 Cipro® BID subjects developed nausea, the other had progression to pyelonephritis)

3 Cipro XR patients were hospitalized during the course of the study (1 each: increased edema in the legs, bowel obstruction. and renal stones). 2 patients in the Cipro® BID group were hospitalized (1 each: alcoholic cardiomyopathy and appendicitis). The distribution of actions taken for AEs was similar between the two groups.

187/200 (93.5%) of AEs in the Cipro XR and 145/166 (87.3%) AEs for the Cipro® BID group either resolved or improved. The remaining 6.5% or 13 AEs on the Cipro XR arm and 15 or 9% of AEs reported in patients treated with Cipro® BID remained unchanged. Included were 1 severe AE on the Cipro XR arm (accidental on-the-job injury) and 3 severe AEs in the Cipro® BID group (back pain, constipation, and unintended pregnancy). None of these were reported as related to study drug.

Drug-Related Adverse Events

There were 46/444 Cipro XR treated subjects with drug-related AEs (10%) as compared to 41/447 (9%) of Cipro® BID patients. The largest number of drug-related AEs involved the digestive system (5% of patients treated with Cipro XR and 2% of patients treated with Cipro® BID, the urogenital system (2% vs. 4%, respectively), and the body as a whole (2% of patients in each group). AEs judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of Cipro XR-treated patients were nausea (3%) and headache (2%).

Of note were the photosensitivity reaction in 1 Cipro XR subjects (eyes hurt when out in the sunshine, even with sunglasses on starting on treatment day 2 and continuing for 3 days and not accompanied by a skin reaction), the 3 episodes of rash, 2 episodes of pruritus, and the episodes of maculopapular and vesiculobullous rash reported from the Cipro XR subjects as compared to only 2 reports of rash from the Cipro® BID subjects. Only 1 of these events was considered a serious AE (1 report each of intense pruritus, excoriations, and generalized papules). These events were considered related to treatment, led to discontinuation of treatment, and required steroids The MO requested that the applicant supply the data on the remaining subjects for review. This data was submitted on 5/9. A review of all subjects reporting rash and/or itching revealed 7 subjects treated with Cipro XR accounting for 12 events, all related to treatment and all of mild to moderate severity. In all cases the event resolved. All subjects had either pruritus alone or in association with a maculopapular rash excluding 1 who had a vesiculobullous oral eruption. One subject complained of sun sensitivity not associated with a rash (eyes hurt in sunshine). On the Cipro® BID arm, there were 2 subjects (3

AEs) with unspecified rash, all related to treatment, mild to moderate in nature and in both cases the events resolved. Thus in this limited sample size, more Cipro XR subjects developed a rash as compared to the comparator arm. Due however to the small sample size, no conclusions could be drawn regarding the potential for increased risk of rash in subjects receiving a newer formulation of ciprofloxacin.

Also of note were the 3 episodes of dizziness attributable to treatment of the Cipro XR arm as compared to the 1 episode on the Cipro® BID arm.

Dizziness was reported in 6 (1%) patients treated with Cipro XR (4 patients were between the ages of 18 to 44 years, 1 patient between 45 to 64 years, and 1 patient was ≥ 75 years). Two (1%) of 134 patients treated with Cipro XR in phase I studies also reported dizziness as an AE. Dizziness also led to early discontinuation of study drug for 3 (<1%) out of 394 patients enrolled in Study 100275 (ongoing, still blinded study) by 30 November 2001.

Table 26
Drug-Related Adverse Events By Body System
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Adverse Event		
Any Body System		
Any Event	46 (10%)	41 (9%)
Body As A Whole		
Any Event	11 (2%)	10 (2%)
Headache	7 (2%)	3 (<1%)
Moniliasis	2 (< 1%)	1 (<1%)
Abdominal Pain	1 (<1%)	2 (< 1%)
Photosensitivity Reaction	1 (<1%)	-
Asthenia	-	3 (<1%)
Leg Pain	-	1 (<1%)
Digestive System		
Any Event	22 (5%)	8 (2%)
Nausea	12 (3%)	4 (<1%)
Diarrhea	4 (<1%)	2 (< 1%)
Dyspepsia	3 (<1%)	-
Vomiting	2 (< 1%)	-
Constipation	1 (<1%)	2 (< 1%)
anorexia	1 (<1%)	1 (<1%)
Flatulence	1 (<1%)	-
Thirst	1 (<1%)	-
GI disorder	-	1 (<1%)
GGT Increased	-	1 (<1%)
Heme and Lymphatic		
Any Event	-	1 (<1%)
Anemia	-	1 (<1%)
Musculoskeletal		
Any event	-	2 (< 1%)
Arthralgia	-	1 (<1%)
Myalgia	-	1 (<1%)
Nervous System		
Any Event	7 (2%)	4 (<1%)
Dizziness	3 (<1%)	1 (<1%)
Depersonalization	1 (<1%)	-
Hypertonia	1 (<1%)	1 (<1%)
Incoordination	1 (<1%)	-
Somnolence	1 (<1%)	2 (< 1%)
Skin And Appendages		
Any Event	6 (1%)	3 (<1%)
Rash	3 (<1%)	2 (< 1%)

Table 26
Drug-Related Adverse Events By Body System
Valid for Safety Population

	Cipro XR N = 444	Cipro®BID N = 447
Adverse Event		
Pruritus	2 (< 1%)	-
Maculopapular Rash	1 (<1%)	-
Vesicolobullous Rash	1 (<1%)	-
Skin Disorder	1 (<1%)	-
Acne	-	1 (<1%)
Special Senses		
Any Event	1 (<1%)	1 (<1%)
Taste Perversion	1 (<1%)	1 (<1%)
Urogenital System		
Any Event	9 (2%)	17 (4%)
Vaginitis	4 (<1%)	7 (2%)
Vaginal Moniliasis	4 (<1%)	10 (2%)
Dysmenorrhea	1 (<1%)	0
Leukorrhea	-	3 (<1%)

3 patients in the Cipro XR group had severe drug-related AEs (2 headache and 1 nausea), while 6 patients in the Cipro® BID group had severe drug-related AEs (3 headache, 1 nausea and diarrhea, 1 vaginitis, and 1 vaginal moniliasis).

Of the 46 patients with drug-related AEs in the Cipro XR group, 44 patients had resolution of their events, 1 improvement (pruritus), and 1 no change (flatulence). Similarly, 1 of the 41 patients with drug-related AEs in the Cipro® BID group had no change in her event (anemia, with a decrease in her hemoglobin from 10.7 g/dL at the pre-therapy visit to 9.8 g/dL at the TOC) during the course of the study, 1 improvement (vaginitis), 37 resolution, and 2 had an insufficient period of follow-up of their events (1 abdominal pain and 1 increased GGT).

Serious Adverse Events

There were no patient deaths during this study. 13 SAEs (in 12 patients, 6 patients in each group) were reported for other reasons, 6 (1%) in the Cipro XR group and 7 (2%) in the Cipro® BID group. 7/13 SAEs were unintended pregnancies (3 in the Cipro XR group and 4 in the Cipro® BID group). 2 of these pregnancies are still ongoing as of the date of this summary and one resulted in the birth of a normal full-term infant. The remaining 4 pregnancies ended with spontaneous abortion. All 4 abortions were reported as unrelated to study drug. The MO requested further details on these cases from the applicant on 9/3/02 and was informed on 9/10/02 that in patients 5013, 6020 and 16007 spontaneous abortions were reported in RDE (Remote Data Entry). According to site personnel, patient 34010 stated later that she had an abortion. There was no information on the fetuses.

Other SAEs in the Cipro XR group were peripheral edema, intestinal obstruction and kidney calculus, and in the Cipro® BID, infection (appendicitis), abortion (spontaneous) and cardiomyopathy. None of the SAEs were considered drug-related.

Clinical Laboratory Tests

Routine hematology, clinical chemistry, pregnancy and urinalysis tests were performed before treatment, at the TOC visit (Day + 4 to + 11), and, if applicable, at the time of premature discontinuation of treatment. Serum theophylline level and prothrombin time (PT) were measured if indicated (patients receiving concomitant theophylline or warfarin).

Percentage of Subjects with Abnormal Test Results

The incidence of abnormal laboratory results was low and consistent between the two groups and the incidence rates of treatment-emergent high and low laboratory abnormalities were comparable between the two treatment groups.

Regarding microscopic hematuria, 4/16 (25%) patients in the XR group and 4/13 (31%) patients in the BID group were normal at pre-therapy but abnormal at TOC. The central lab utilised 0 - 8 (RBC/HPF) for females as the range of normal for urine RBCs (any counts above 8 were considered abnormal). 53/69 (77%) patients in the XR group and 29/42 (69%) patients in the BID group were abnormal at pre-therapy and 21/69 (30%) patients in the XR group and 17/42 (40%) patients in the BID group continued abnormal at the TOC. In addition, the two groups had a similar incidence of positive urinary blood by dipstick (11%) for normal at pretherapy and abnormal at TOC.

Medical Officer's Comment: *As expected in the population under treatment, microscopic hematuria was noted in similar numbers both pre and post-therapy between treatment arms. No data was collected with regards to menses in these subjects.*

Patients with Clinically Significant Laboratory Abnormalities and changes from baseline:

The highest incidence of such changes was 5/417 (1%) for ALT and 3/420 ≥ 1.8 times the upper limit of normal in the Cipro XR group as compared to 2/421 (< 1%) for ALT in the Cipro® BID group. There was 1 Cipro XR (<1%) patient that had a treatment-emergent elevation of hepatic transaminases (SGPT and SGOT) more than 3 times the upper limit of normal. This patient had one AE, which was a bacterial infection ("streptococcal throat") not related to study drug. None of the patients had concurrent increases of bilirubin.

Table 27
Incidence of Clinically Significant Hepatic Transaminase Abnormalities
Valid for Safety Population

Laboratory Variable	Criterion	Cipro XR		Cipro® BID	
SGPT (ALT)	≥ 1.8 x Upper Limit of nl	5/417	1	2/421	<1
	> 3 x Upper Limit of nl	1/423	<1	0/426	0
SGOT (AST)	≥ 1.8 x Upper Limit of nl	3/420	1	0/414	0
	> 3 x Upper Limit of nl	1/422	<1	0/418	0
Total Bilirubin	≥ 1.8 x Upper Limit of nl	0/426	0	0/430	0
	> 3 x Upper Limit of nl	0/427	0	0/430	0

VII. Use in Special Populations:

Gender

All patients in this study were female.

Age

Patients in this study ranged in age from 18 to 79 years old (mean 35). Only 5 subjects were > 65.

Ethnicity

The majority of patients in the study were white (79%). Patients of other ethnic origins were represented (9% Black, 9% Hispanic, 2% Asian).

Medical Officer's Comment: *Although subjects of other ethnic backgrounds other than Caucasian were poorly represented, it seems unlikely that Cipro XR will have different efficacy or safety in such groups given the known effects of the parent compound ciprofloxacin.*

Other Conditions Related to Safety

Pregnancy

There were 7 pregnancies (3 in the Cipro XR group and 4 in the control group). According to a global standard operating procedure for the handling of SAEs at Bayer Pharma each pregnancy occurring at any time after a patient's formal entry into a study until the end of the follow-up period as defined in the respective study protocol must be reported by the investigator as an SAE.

All 7 patients who became pregnant had at least a negative urine pregnancy test at baseline and reported use of at least two methods of contraception during exposure to study drug. Two of these pregnancies are still ongoing as of the date of the submission and one resulted in the birth of a normal full-term infant. The remaining 4 pregnancies ended with spontaneous abortion. One abortion was reported as an SAE, 2 were reported as AEs, and the fourth was reported in the comment section of the AE page of the patient's electronic CRF. All 4 abortions were reported as unrelated to study drug.

Pediatric Database

No patients below 18 years of age were enrolled in Study 100346, any of the phase I studies, or Study 100275 by 30 November 2001.

Clinical Pharmacology Studies

49 volunteers received at least one dose of Cipro XR 500 mg tablets and 85 volunteers received at least one dose of Cipro XR 1000 mg tablets.

The overall incidence rate for any event was 24% for the Cipro XR 500 mg tablet and 18% for the Cipro XR 1000 mg tablet. AEs were reported in 16% (5/31) of volunteers who received at least one dose of Cipro® 250 mg BID. The most commonly reported AE associated with the Cipro XR 500 mg tablet was headache, with an incidence rate of 10%. For the Cipro XR 1000 mg tablet, the most common AE was rhinitis, with an incidence rate of 6%. Rhinitis was also reported in 6% of volunteers who received Cipro XR 500 mg tablet. Most events were considered to be unrelated to study drug, and all but one (thigh laceration secondary to a motorcycle accident) were described as mild to moderate in intensity. There were 3 study dropouts due to AEs, none of which were related to study drug (2 injuries, I GI event).

For Cipro XR 500, abnormal laboratory results occurring more than 5% were observed for elevated potassium (10%), elevated WBC count (6%), increased PTT (16%), low calcium (11%), low BUN (18%), low serum creatinine (6%), low total protein (21%), low GGT (6%), low LDH (44%), low cholesterol (8%), and low triglycerides (7%). Similar trends were observed for treatments with Cipro XR 1000 mg QD, Cipro® 250 mg BID and Cipro® 500 mg BID. None of the laboratory abnormalities exceeded 3x the upper limit of normal or acceptable lower limits of normal.

There were no remarkable abnormal findings in the phase I studies related to the safety and tolerability of Cipro XR either 500 mg or 1000 mg tablets. Most of the reported AEs were considered to be unrelated to study drug, and all drug-related AEs were mild to moderate in intensity. The three AEs that resulted in study discontinuation occurred during washout periods, and were deemed unrelated to study drug.

CUTI study:

The submission consisted of listings of premature discontinuations of study drug due to AEs, deaths, and other SAEs in patients enrolled by 30 November 2001. As of that date, a total of 394 patients were enrolled in this study. The overall incidence of AEs was 31% for the two blinded groups. The most frequent events were headache and nausea (4% each), followed by dizziness (3%), then abdominal pain, dyspepsia, diarrhea, constipation, and back pain (2% each).

21 patients discontinued study drug therapy prematurely due to AEs. Events leading to discontinuation included dizziness (3), bradycardia with double vision (1), headache (1), increased asthenia (1), nausea (1), vomiting (1), constipation (1), dyspepsia (2), abdominal pain (1), sepsis (2), hypotension (1), dehydration (1), worsening urinary retention (1), abnormal liver function tests (2), abnormal kidney function tests, amylase and uric acid (1), coronary artery occlusion (1), and gonorrhea (1).

There was one death (Study 100275, Center 049, Patient 49015) reported during the period up to 30 November 2001. The patient was a 95-year-old white male with CUTI and a history of multiple medical problems including prostate cancer with subsequent transurethral resection, bladder outlet obstruction, urinary retention, and arteriosclerotic cardiovascular disease. His baseline renal indices were normal. It was confirmed that he received study drug for at least 5 days, but possibly up to 7 days (last 2 days could not be confirmed, because medication bottles were never returned). The patient was transferred to two facilities (hospital and nursing home) before expiring from acute renal failure on 25 August 2001. A hospital discharge summary states that on 20 August 2001, the patient's BUN was 53 mg/dL and his creatinine was 5.1 mg/dL.

A second death (Study 100275, Center 052, Patient 52008) occurred 3 days after the stated period above (03 December 2001) and is included in this summary due to the nature of the outcome. This patient was an 89-year-old white female with CUTI and a previous history of cardiovascular disease. Thirty-four days after completion of study drug therapy, she developed respiratory failure secondary to congestive heart failure and succumbed. No aggressive measures were undertaken due to a "do not resuscitate" order per patient's and family's wishes.

A total of 24 (6.1%) patients experienced SAEs, and within this population, the 2 deaths occurred. These primary events were as follows: chest pain (2); rectal bleeding (2); abdominal pain (1); removal of a benign lung mass (1); prostate resection (1); acute renal failure with hematuria (1); dehydration (1); sepsis (3); worsening UTI (1); respiratory failure (1); myocardial infarction or coronary artery occlusion (2); coronary artery disease with subsequent coronary artery bypass, post-operative hemorrhage and asthma (1); hypertension, headache and UTI, subsequently diagnosed as bladder carcinoma (1); hypotension (1); back muscle spasms (1); hip replacement (1); cellulitis of the hand (1); and acute lymphocytic leukemia (1). However, of these 24 patients, only 7 had premature discontinuation of study drug because of the following: hypotension (1),

hypertension and urosepsis (1), possible sepsis (1), coronary artery occlusion (1), severe abdominal pain (1), severe vomiting (1), and diarrhea with malaise (1).

There were no safety alerts to report to the FDA from the date of first patient enrollment on 15 April 2001 to 30 November 2001. However, on 25 January 2002, Bayer became aware of one case of perforated duodenal ulcer (Study 100275, Center 082, Patient 82025). This patient is a 34-year-old Hispanic female who was enrolled in the study for acute, uncomplicated pyelonephritis. She was treated with Cipro® 500 mg BID from 19 December 2001 to 29 December 2001 (blind was broken in this case). On 08 January 2002, she presented to the emergency room with a one-week history of severe midepigastric pain. She underwent repair of a perforated duodenal ulcer on 09 January 2002. The etiology of the ulcer was not ascertainable during her hospitalization.

Safety conclusions:

Cipro XR and Cipro®BID, both given for 3 days for the treatment of uncomplicated UTI, exhibited similar safety profiles. No clinically meaningful differences were found between the two formulations of ciprofloxacin.

121/444 (27%) of patients treated with Cipro XR and 105/447 (23%) of patients treated with Cipro®BID reported at least one AE during the course of the study.

The body system with the highest percentage of AEs regardless of relationship to study drug was the body as a whole for both Cipro XR and Cipro®BID groups (11% vs. 9%). AEs occurring in 2% or more of patients in either the Cipro XR or the control group in this system were headache (4% vs. 3%) and abdominal pain (1% vs. 2%).

The incidence of digestive system AEs was higher in the Cipro XR group (9% vs. 3%). Nausea was the most common event in this system, occurring in 4% of patients treated with Cipro XR and 2% of patients treated with Cipro®BID. The incidence of all other AEs in any body system was comparable between the two groups.

There were 46/444 Cipro XR treated subjects with drug-related AEs (10%) as compared to 41/447 (9%) of Cipro® BID patients. The largest number of drug-related AEs involved the digestive system (5% of patients treated with Cipro XR and 2% of patients treated with Cipro® BID), the urogenital system (2% vs. 4%, respectively), and the body as a whole (2% of patients in each group). AEs judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of Cipro XR-treated patients were nausea (3%) and headache (2%).

8/200 (4%) of AEs in the Cipro XR group and 2/166 (1%) of AEs in the Cipro® BID group resulted in discontinuation of study drug. The events that led to discontinuation occurred in 2 (<1%) patients for each of the two treatment groups (1 Cipro XR subjects developed abdominal pain, back pain, nausea, vomiting and Dysuria, the other developed a maculopapular rash, pruritus and excoriations, 1 Cipro® BID subject developed nausea, the other had progression to pyelonephritis).

There were no patient deaths during this study. 13 SAEs (in 12 patients, 6 patients in each group) were reported for other reasons, 6 (1%) in the Cipro XR group and 7 (2%) in the Cipro® BID group. 7/13 SAEs were unintended pregnancies (3 in the Cipro XR group and 4 in the Cipro® BID group). 2 of these pregnancies are still ongoing as of the date of this summary and one resulted in the birth of a normal full-term infant. The remaining 4 pregnancies ended with spontaneous abortion. All 4 abortions were reported as unrelated to study drug. Other SAEs in the Cipro XR group were peripheral edema, intestinal obstruction and kidney calculus, and in the Cipro® BID, infection (appendicitis), abortion (spontaneous) and cardiomyopathy. None of the SAEs were considered drug-related.

The incidence of abnormal laboratory results was low and consistent between the two groups.

VIII. Recommendations

A. Recommendations

The reviewing medical officer recommends:

1. Approval of Cipro XR for the indication of treatment of uncomplicated urinary tract infection (UTI) caused by *Escherichia coli, Enterococcus faecalis*, and *Proteus mirabilis.*

2. There was an insufficient number of uncomplicated urinary tract infections due to *Klebsiella pneumoniae* and *Staphylococcus saprophyticus* to support the indication for treatment of this organism, therefore this indication should not be granted for these pathogens.

B. Label Review

The portion of the label for this indication should be amended to read as follows:

CIPRO XR is indicated solely for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms as listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli, Proteus mirabilis,* and *Enterococcus faecalis.*

C. Phase IV Commitments

There are no Phase IV commitments for this indication; however, ongoing discussions between the FDA and the applicant regarding the appropriate use of Cipro XR only in urinary tract infections should continue.

RECOMMENDED REGULATORY ACTION:

Ciprofloxacin XR should be approved for the treatment of uncomplicated urinary tract infections (acute cystitis)

Regina Alivisatos, MD
Medical Officer, HFD-590

Concurrence Only:
Div. Dir/Albrecht

Cc: Orig. NDA 21-473
Division File
HFD-590/MTL/Roca
HFD-590/MO/Ruiz
HFD-590/CSO/Saliba
HFD-590/Stat/Davi
HFD-590/Micro/Bala
9/13/02

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Regina Alivisatos
12/11/02 10:13:08 AM
MEDICAL OFFICER

Rigoberto Roca
1/7/03 01:18:08 PM
MEDICAL OFFICER

Renata Albrecht
1/7/03 05:54:33 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21- 473
4 Month Safety Update
CIPRO XR (formerly known as Cipro (b) (4) and Cipro (b) (4)

Indication: Ciprofloxacin XR 500 mg tablets are indicated in the treatment of uncomplicated urinary tract infection (acute cystitis) caused by *Escherichia coli*, (b) (4) *Proteus mirabilis, Staphylococcus saprophyticus*, or *Enterococcus faecalis* in women.

Applicant: Bayer Pharmaceutical Division

Address: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Date of Submission: June 28, 2002
CDER Stamp date: June 30, 2002
Date Submission received by reviewer: July 6, 2002
Date Review Begun: July 9, 2002
Date Review Completed: July 11, 2002

Drug Name: Ciprofloxacin Hydrochloride and Ciprofloxacin

Proprietary Name: CIPRO XR

Pharmacologic Category: Fluoroquinolone

Dosage Form: Tablets

Route of Administration: Oral

Strength: 500 mg tablets

Safety Update:

NDA 21-473 for the modified release formulation of ciprofloxacin (CIPRO XR 500 mg tablets) was submitted on March 4, 2002. The ISS in the NDA presented safety data on 891 patients enrolled in a single pivotal clinical trial that evaluated the safety and efficacy of CIPRO XR 500 mg tablets in the treatment of women with uncomplicated urinary tract infections. Also included in the ISS was safety data on 138 patients from 8 phase I studies, 3 of which were conducted with CIPRO XR 500 mg tablets (51 patients total) and 5 with CIPRO XR 1000 mg tablets (51 patients total). Safety data on 394 patients enrolled in an ongoing clinical trial (Study 100275) evaluating the safety and efficacy of CIPRO XR 1000 mg tablets in the treatment of patients with CUTI or acute uncomplicated pyelonephritis were included in the NDA.

In the original safety database of 891 subjects, the incidence of AEs in patients treated with Cipro XR 500 mg was 27%. The body as a whole was the body system with the highest percentage (11%) of AEs. Most (93.5%) AEs were mild to moderate in intensity. No single AE was considered severe in more than 2 patients. Adverse events occurring in at least 2% of patients treated with Cipro XR 500 mg were headache (4%) and nausea (4%).

Drug-related AEs were reported in 10% of patients, with nausea (3%) and headache (2%) being the only two drug-related AEs occurring in 1% or more of patients. Only 1 (flatulence) of 45 drug-related AEs in the Cipro XR 500 mg group remained unchanged. All other drug-related AEs either resolved or improved.

No patient deaths occurred during the study. Two patients (<1%) were withdrawn early due to an AE and 6 patients (1%) experienced SAEs. The incidence of laboratory test abnormalities, especially clinically significant abnormalities, was low. Descriptive statistics of changes in laboratory test results from baseline did not show any trend that appeared to be uniquely associated with Cipro XR 500 mg.

Based on the safety profile of Cipro XR 500 from the pivotal study, the additional safety information available from clinical pharmacology studies, and the long-term clinical experience with ciprofloxacin it was concluded that Cipro XR given as 500 mg every 24 hours for 3 days was safe for use for the treatment of uncomplicated urinary tract infections (acute cystitis).

The reporting period for this update is from December 21, 2001 through May 1, 2002. No new studies with either modified release formulation have been instituted and the safety update provided no new safety information for the 500 mg tablet. Only safety information from 619 subjects enrolled in the ongoing clinical trial (Study 100275) with CIPRO XR 1000 mg tablets in CUTI and acute, uncomplicated pyelonephritis were included in the submission.

350/619 (56%) of the patients were female and 269/619 (44%) were male. They ranged in age from 18 to 95 years, with a mean of 60.0 years. The majority (80%) was white, 11% were black, 8% were Hispanic, and < 1% were Asian. The mean weight was 76.5 kg.

220/619 (36%) of patients had at least one AE reported The body systems with the highest percentages of AEs regardless of relationship to study drug were the digestive system (89/619; 14%) and the body as a whole (80/619; 13%). Incidence rates of AEs for other body systems were as follows: urogenital system, 8% (49/619); nervous system, 6% (35/619); respiratory system, 5%; cardiovascular system, 4%; hemic and lymphatic, metabolic and nutritional, skin and appendages, and musculoskeletal systems, 2% each (11/619); and special senses, 1%.

The most frequent AEs headache and nausea occurred in 5% of patients each (31/619 and 34/619), followed by diarrhea in 17/619 (3%), vomiting in 13/619 (2%),

dyspepsia 10/619 (2%), and dizziness 18 (3%). All other events occurred in $\leq 1\%$ of patients. Events of note included abnormal LFTs in 9/619 (1%) patients and rash in 2/619 subjects. There were no episodes of seizure activity, arthritis, or tendonitis.

At least one drug-related AE was reported in 14% (89/619) of patients. The body system with the highest percentage of drug-related AEs was the digestive system (56/619; 9%) followed by the nervous system (11/619; 2%) and the urogenital system (14/619, 2%). The most frequently reported drug-related AEs were nausea in 21/619 (3%) of patients; headache and diarrhea in 12/619 (2%) of patients each, dyspepsia in 8/619 (1%) and abnormal LFTs and dizziness in 7/619 (1%) each.

Two deaths in Study 100275 (patient 49015 center 049 died of ARF secondary to bilateral ureteral obstruction as evidenced by a renal ultrasound, most likely due to metastatic prostate cancer and patient 52008 center 052 died of respiratory failure due to CHF) were reported in the original NDA and there were no additional deaths reported in the update.

39/619 (6%) of subjects had serious AEs. 2% involved the body as a whole, 1% the cardiovascular system and 1% the urogenital system. The rate for all other systems was lower than 1%. No single serious AE occurred at a rate of 1% or higher. Only 1 serious AE was considered possible drug related (small intestinal perforation occurring on study day 21, post treatment).

30/619 (5%) patients discontinued treatment due to an AE. The digestive system had the highest rate of events leading to premature discontinuation of treatment (2%). The incidence of any single event within the digestive system leading to discontinuation was under 1%. 13 of the AEs that led to discontinuation were considered severe. 4 of these were related to LFT abnormalities, the remainder included 1 event each of urinary retention, nausea, vomiting, diarrhea, dyspepsia, hematuria, and laryngeal neoplasia as well as 2 events of headache. For all other body systems, the rate of any event was 1% or lower. Of note however, was that 3 subjects discontinued prematurely due to increased LFTs. These elevations were described as drug-related and severe in 2 subjects and moderate in 1. Overall, the incidence of drug-related AEs leading to discontinuation of treatment was 3% (17/619).

A review of the subjects with LFT abnormalities revealed a subject with increased ALT and AST to > 10 x ULN associated with an increased bilirubin (Baseline SGOT/SGPT: 13/13; Day 4 of R/x: 609/588; Day 7: 13/35; Baseline bilirubin 0.3; Day 4: 3.2; Day 7: 0.8). The other 2 subjects who prematurely discontinued treatment due to abnormal LFTs had AST and ALT elevation to 2 – 3 x ULN without concurrent increases in bilirubin.

A review of clinical laboratory abnormalities did not reveal any abnormalities inconsistent with underlying disease status. 12/546 (2%) of subjects had a SGPT (ALT) =1.8 x ULN and 11/557 had values > 3 x ULN. Similarly, 12/543 (2%) had SGOT (AST) =1.8 x ULN and 8/551 (1%) had values > 3 x ULN. Only 1 subject had a total bilirubin of 1.8 x ULN and none were > 3 x ULN.

7/11 patients with treatment-emergent elevation of SGPT (ALT) and 4/8 patients with treatment-emergent elevation of SGOT (AST), both >3 x ULN had abnormal corresponding baseline values (1.1 to 2.8 and 1.1 to 2.9 x ULN respectively). Treatment-emergent elevations of both SGPT and SGOT >3 x ULN were considered related to study drug in 3 patients, including one patient whose study drug treatment was discontinued because of such elevations. Only one patient with treatment-emergent elevation of SGPT had nausea and vomiting. All other patients had no AEs related to elevated hepatic transaminases.

Conclusions and Recommendations:

Blinded AE data from an ongoing study of CIPRO XR 1000 mg once daily for 14 days in the treatment of CUTI form 619 patients were consistent with those previously reported in the ISS for patient treated with CIPRO XR 500 mg once daily for 3 days for uncomplicated urinary tract infections and did not reveal any unusual rates of AEs or unexpected AEs. There appeared to be a higher incidence of LFT abnormalities in the current dataset that remains to be further reviewed when the data are unblinded. There are no ongoing studies with the CIPRO XR 500 mg formulation and no changes to the conclusion previously drawn regarding the safety of that formulation in an adult population suffering from uncomplicated UTI.

The MO continues to recommend approval of Cipro XR 500 mg for the indication of treatment of uncomplicated urinary tract infection (UTI) caused by *Escherichia coli, Enterococcus faecalis*, and *Proteus mirabilis*.

Regina Alivisatos, MD
Medical Officer, HFD-590

Concurrence Only:
Acting Div. Dir HFD-590/AlbrechtR

Cc: Orig. NDA 21-473
Division File
HFD-590/MTL/Roca
HFD-590/MO/Ruiz
HFD-590/CSO/Saliba
HFD-590/stat/Davi
HFD-590/micro
9/9/02

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Regina Alivisatos
12/11/02 10:24:03 AM
MEDICAL OFFICER

Rigoberto Roca
1/7/03 01:21:31 PM
MEDICAL OFFICER

Renata Albrecht
1/7/03 05:00:23 PM
MEDICAL OFFICER

ADDENDUM to Medical Officer's Review of NDA 21- 473
CIPRO XR (formerly known as Cipro (b) (4) and Cipro (b) (4)

Applicant: Bayer Pharmaceutical Division

Address: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Date of Submission: November 26, 2002
CDER Stamp date: November 30, 2002
Date Submission received by reviewer: November 26, 2002
Date Review Begun: December 2, 2002
Date Review Completed: December 3, 2002,

Drug Name: Ciprofloxacin Hydrochloride and Ciprofloxacin

Proprietary Name: CIPRO XR

Pharmacologic Category: Fluoroquinolone

Dosage Form: Tablets

Route of Administration: Oral

Strength: 500 mg tablets

Background: Bayer submitted NDA 21-473 on March 4, 2002. The requested indication was for the use of Cipro XR 500 mg PO QD for 3 days in the treatment of uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli,* (b) (4) *Proteus mirabilis, Staphylococcus saprophyticus,* and *Enterococcus faecalis* .

The clinical data were derived from a phase III, prospective, active-controlled, randomized, double blind, multicenter study (Study 100346 Cipro XR 500 mg PO QD x 3 days vs. Cipro 250 mg PO BID x 3 days) conducted in the United States in adult female patients (ages 18 to 65 years) with uncomplicated urinary tract infections. 905 women were enrolled and 891 (444 in the Cipro XR group and 447 in the Cipro® BID group) received at least one dose of study drug and were included in the valid for safety population. 422 patients (199 in the Cipro XR group and 223 in the Cipro® BID group) fulfilled the criteria for the valid for efficacy population. The treatment groups were similar with respect to baseline demographic variables and infection characteristics. The primary efficacy variable was microbiologic outcome at the test-of-cure (TOC) visit. Secondary efficacy variables included clinical response at the TOC, as well as microbiologic and clinical outcomes at the late follow-up visit. Analyses were performed on the subset of valid patients and on the ITT population.

Cipro XR for 3 days was non-inferior to Cipro® BID for 3 days with respect to the primary and secondary efficacy parameters and was effective against infections caused by the predominant group of pathogens causing uncomplicated urinary tract infections.

Microbiologic Outcome of Original Causative Organism at the TOC Valid for Efficacy Population

	Cipro XR N = 199 (204 Original Organisms)	**Cipro®BID N = 223 (239 Original Organisms)**
	Eradication N (%)	**Eradication N (%)**
Escherichia coli	156/160 (97.5%)	176/181 (97%)
Enterococcus faecalis	10/11 (91%)	17/21 (81%)
Klebsiella pneumoniae	7/9 (78%)	11/14 (79%)
Proteus mirabilis	11/12 (92%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83%)	7/7 (100%)

Based on the above, the MO recommended approval of Cipro XR 500 mg QD x 3 days to treat uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli, Enterococcus faecalis,* and *Proteus mirabilis.* There were an insufficient number of uncomplicated urinary tract infections due to *Staphylococcus saprophyticus* and *Klebsiella pneumoniae* to support the indication for treatment of these organisms.

The above were communicated to the sponsor in a FAX on November 22, 2002 and discussed with representatives of BAYER on November 25, 2002. The applicant submitted a formal response on November 26, 2002 with a CDER stamp date of November 29, 2002. In that response, the applicant stated that they would like to retain *Staphylococcus saprophyticus* and *Klebsiella pneumoniae* in the first list in the **MICROBIOLOGY** section and in the approved organisms under the **INDICATIONS AND USAGE** section for the following reasons:

Applicant Rationale for *Klebsiella pneumoniae*:

The 100346 study results show that the microbiological success rate in patients having an infection with *K pneumoniae* was 7/9 (78%) for the Cipro XR treatment group. This

success rate is comparable to that of ciprofloxacin immediate-release tablets (11/14 [79%]).

E coli is the predominant organism in uncomplicated urinary tract infections, although *K pneumoniae* is also recovered. When using $\geq 10^5$ CFU/mL, nine patients in the Cipro XR group were identified where *K pneumoniae* was the causative organism. When using $\geq 10^4$ CFU/mL, an additional six patients in the Cipro XR group were identified. These patients were all treatment successes. Including these patients, the eradication rate is 13/15 (87%), which provides additional reassurance of the efficacy against this organism.

Additionally, given the high urine concentrations of Cipro XR (see graph under *S saprophyticus* rationale) that are maintained throughout the dosing interval and the MIC_{90} of *K pneumoniae* (0.25 µg/mL), Cipro XR would be expected to be effective in treating uncomplicated urinary tract infections due to this pathogen.

Applicant Rationale for *Staphylococcus saprophyticus*:

Ciprofloxacin is active against *Staphylococcus saprophyticus* and maintains urine concentrations significantly above the minimum inhibitory concentration (MIC_{90} = 0.50) for this organism throughout the dosing interval.

Ciprofloxacin 100 mg immediate-release tablets (BID x 3 days) are approved for acute cystitis due to *Staphylococcus saprophyticus.* Based on data from previous clinical pharmacology studies (e.g., conventional 100 mg tablet data) and conventional 250 mg BID tablet / 500 mg QD modified-release data, the urinary concentrations of ciprofloxacin following different doses are shown in the graph below.

The 100346 study results show that the microbiological success rate in patients having an infection with *S saprophyticus* was 6/7 (86%) for the Cipro XR treatment group for colony counts $\geq 10^5$ CFU/mL, and 7/8 (88%) for colony counts $\geq 10^4$ CFU/mL. We note from the NDA review that levofloxacin was approved for this organism in this indication with a success rate of 9/11 (82%), which is not appreciably different from the Cipro XR results, and that results from colony counts as low as 10^3 were included in the analysis.

The urine concentration for the Cipro XR formulation remains substantially above the MIC for *S. saprophyticus* for the full 24 hour dosing interval. Although there were less than 10 isolates of *S saprophyticus* in the 100346 study in the Cipro XR arm, we would expect that from a PK/PD perspective that the Cipro XR product would perform at least as well or better than the 100 mg bid product, which is approved for Acute Cystitis due to *S. saprophyticus*. Also, in the 100346 study, the 250 mg BID ciprofloxacin immediate release arm had a success rate of 7/7, 100%, which provides further evidence that Cipro XR would be an effective agent for this pathogen.

The excellent clinical and bacteriologic efficacy responses for this organism in the Cipro 100 mg bid x 3 days from the immediate-release SNDA studies provide reassurance that a Cipro XR 3 day treatment course would also be efficacious.

Discussion:

In generating a decision regarding the approvability of selected pathogens for an indication multiple factors are considered including but not limited to regulatory precedence, regulatory guidance documents including the 1992 Points to Consider document, MIC data, and PK/PD data.

At the present time, immediate release ciprofloxacin is NOT APPROVED for the treatment of Acute Uncomplicated Cystitis in females caused by *Klebsiella pneumoniae.* The current indication in labeling is a s follows:

Ciprofloxacin: Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.*

The following quinolone antimicrobials have been approved for the treatment of uncomplicated urinary tract infections caused by either *Staphyloccus saprophyticus or Klebsiella pneumoniae.* In addition, trovafloxacin was not approved for either pathogen.

Levaquin®: Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus*

Floxin®: For uncomplicated urinary tract infection caused by *Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis or Pseudomonas aeruginosa.*

Maxaquin®: For uncomplicated urinary tract infection caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Staphylococcus saprophyticus.*

Noroxin®: For uncomplicated urinary tract infection caused by *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Citrobacter freundii, Enterobacter* aerogenes, *Enterobacter cloacae, Proteus vulgaris, Streptococcus agalactiae.*

Penetrex®: For uncomplicated urinary tract infection caused by *Escherichia coli, Staphylococcus epidermidis* and *Staphyloccus saprophyticus.*

Tequin®: Uncomplicated UTI (cystitis) due to *Escherichia coli, Proteus mirabilis,* or *Klebsiella pneumoniae.* (single dose).

Regarding regulatory guidance, the ODEIV guidance for industry document issued on 7/22/98 and presented in the July 1998 AC states the following:

To be included in the study, a subject must have a positive pre-treatment clean-catch midstream urine culture within 48 hours of enrollment in the study, defined as $\geq 10^5$ CFU/mL. Eradication is defined as a urine culture, taken within the 5- to 9-day post-

therapy window, shows that all uropathogens found at entry at $\geq 10^5$ CFU/mL are reduced to $\geq 10^4$ CFU/mL.

Others have recommended using a colony count of $\geq 10^3$ or ^{4} (CID 1992; 15 Suppl: s216-227) but the AC did not agree with this.

Additionally, regarding organism-specific labeling, ODE IV continues to adhere to the 10% Rule, cited in the 1992 Points-to-Consider document

This document addresses the issue of organism-specific labeling as follows:

- The requested organism must be generally considered to be pathogenic in that indication
- The requested organism must represent at least 10% of the evaluable cases OR 10 total (whichever is higher) and
- The eradication rate must be clinically acceptable

When considering organisms for labeling that do not meet the 10% rule, the following additional caveats are to be taken into consideration:

- The *in vitro* activity of the drug versus the pathogen is at least similar to that of other pathogens more substantially evaluated in the clinical trails
- The mechanism of resistance is similar to that of other pathogens more substantially evaluated in clinical trails
- No scientific data exist that suggest difference sin the management of infections due to these pathogens.

A review of the MORs revealed the following:

Levofloxacin NDA 20-634 (AP 1998):

The applicant provided 2 populations for analysis, those as defined in the regulatory guidance and those considered "possible evaluable" with initial colony counts of $\geq 10'^3$. The reviewer accepted a count of $\geq 10'^3$ for *Staphyloccus saprophyticus*. There were 11 cases with *Staphyloccus saprophyticus*. As the sole pathogen. The eradication rate on which the approval was based was 9/11. Of note, it appeared as if 8 cases had initial colony counts of $\geq 10^5$ with an eradication rate of 100%).

Regarding *Klebsiella pneumoniae*: The approval was based on an eradication rate of 10/11. It appeared as if 9 subjects had initial colony counts of $\geq 10^5$ and the eradication rate for these isolates was 8/9 (82%).

Gatifloxacin NDA 21-061 (AP 1999):

An approval for *Staphyloccus saprophyticus* was not granted based on an eradication rate of 6/7 (85.7%) for the single dose regimen and 5/5 for the 3 day regimen. Regarding

Klebsiella pneumoniae, an approval was granted based on 14/14 (100%) for the single dose regimen and 10/12 (83.3%) for the three day regimen.

Conclusions:

Staphylococcus saprophyticus:

A decision was made to grant an approval for this pathogen. The rationale for this decision despite the fact that the minimum requirement of the "rule of 10" was not met included the following:

.

The eradication rate increased to 85.7% (6/7) on the Cipro XR arm with the addition of an additional patient with an isolate from a pretreatment clean-catch midstream urine culture at enrollment with a colony count of $\geq 10^4$ CFU/mL. This level is well accepted in the literature as well as in the current ODEIV guidance document for *Staphylococcus saprophyticus*. This patient was a clinical cure with eradication at the TOC. In addition, there were 2 Cipro® BID patients with similar colony counts and outcomes added to the dataset.

Of great weight in the decision making process was the fact that ciprofloxacin (b) (4) (b) (4) has already been granted an approval for *Staphylococcus saprophyticus*. Both Cipro XR and Cipro (b) (4) are renally excreted and the levels achieved in the urine are easily attainable and very similar between both drugs. These urine concentrations remain above the minimum inhibitory concentration (MIC_{90} = 0.50 mcg/mL) for this organism throughout the dosing interval. However, as the minimum requirement of the Rule of 10 was not met it was requested that and * be added with the following qualifying statement "*safety and efficacy were demonstrated in < 10 patients". A Phase IV commitment of the addition 10 – 20 patients was requested in order to remove this statement.

(b) (4)

FDA recommendations for labeling:

The MO continues to recommend approval of Cipro XR 500 mg for the indication of treatment of uncomplicated urinary tract infection (UTI) caused by *Escherichia coli, Enterococcus faecalis*, and *Proteus mirabilis.*

Representatives of the applicant and the Agency agreed upon the following labeling on December 9. 2002:

INDICATIONS AND USAGE

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli, Proteus mirabilis,* and *Enterococcus faecalis,* or *Staphylococcus saprophyticus**.
*Safety and efficacy were shown in less than 10 isolates.

(b) (4)

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 Cipro BID group. The primary efficacy variable was bacteriological eradication at Test of Cure (Day 4 – 11 Post-therapy).

The bacteriologic eradication and clinical success rates were similar between CIPRO XR and Cipro BID. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO XR minus Cipro BID) 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
Clinical Response at TOC (n/N)*	189/199 (95.0%)	204/223 (91.5%)
	CI [-1.1%, 8.1%]	
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 (100.0%)
S saprophyticus†	6/7 (85.7%)	9/9 (100.0%)

* n/N = patients with pathogen eradicated /total number of patients

† The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria with the exception of *Staphylococcus saprophyticus* where a level of $\geq 10^4$ CFU/mL was considered acceptable

In addition to the above labeling recommendations, an agreement was reached regarding a Phase IV commitment to provide confirmatory evidence of CIPRO XR efficacy in treating uncomplicated UTI caused by *Staphylococcus saprophyticus* by no later than December 31, 2004. in order to remove the * from the label.

Additionally, the applicant will provide an annual update on CIPRO XR usage patterns for the first two years of product availability; with the first submission date being no later than February 28, 2004.

Regina Alivisatos, MD
Medical Officer, HFD-590

Concurrence Only:
Acting Div. Dir HFD-590/AlbrechtR

Cc: Orig. NDA 21-473
Division File
HFD-590/MTL/Roca
HFD-590/MO/Ruiz
HFD-590/CSO/Saliba
HFD-590/stat/Davi
HFD-590/micro/Dionne
12/11/02

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/s/

Regina Alivisatos
12/11/02 10:58:07 AM
MEDICAL OFFICER

Rigoberto Roca
1/7/03 01:24:59 PM
MEDICAL OFFICER

Renata Albrecht
1/7/03 04:54:17 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation III

NDA:	21-473
Generic	Ciprofloxacin
(Brand®)	CIPRO® XR
Dosage Strength	500 mg
Submission Date	March 4, 2002
Applicant:	Bayer
Clinical Division	DSPIDP (HFD-590)
OCPB Division	DPE3 (HFD-880)
Type of Submission	NDA original submission
Reviewer:	Dakshina Chilukuri, Ph.D.
Team Leader	Barbara Davit, Ph.D.
Review Date	December 02, 2002

EXECUTIVE SUMMARY

The applicant is seeking approval of CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin*) tablets containing ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration in NDA 21-473. CIPRO® XR Tablets (sometimes referred to as Ciprofloxacin (b) (4) 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 uncomplicated urinary tract infections caused by aerobic gram-positive such as *Enterococcus faecalis, Staphylococcus saprophyticus* and gram-negative microorganisms such as *Escherichia coli,* (b) (4) *Proteus mirabilis*.

CIPRO® XR is a new (b) (4) once-daily (OD) new tablet formulation of ciprofloxacin with a rapid onset of action. 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.

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.

Eight clinical pharmacology studies were conducted with CIPRO® XR, 3 with the 500 mg tablet, and 5 with the 1000 mg tablet. (Data from the studies on the 1000 mg tablet will be reviewed in support of NDA 21-554, submitted October 29, 2002 for the indication of complicated urinary tract infections). All studies were conducted in healthy young male volunteers. These studies compared the ciprofloxacin pharmacokinetics of

the CIPRO® XR once-daily regimen to the corresponding immediate release regimen (eg, 500 mg MR vs. 250 mg immediate release BID), examined the effects of various meals on the performance of the (b) (4) tablet, and investigated possible drug interactions.

The 24-hour area under the curve (AUC) obtained following administration of 500 mg CIPRO® XR was shown to be equivalent to that attained with BID dosing of 250 mg immediate release ciprofloxacin. The bioavailability of the (b) (4) 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} achieved following administration of the 500 mg (b) (4) tablet is higher than that observed for the 250 mg immediate release tablet, but lower than the C_{max} expected from a 500 mg immediate release tablet. Trough plasma concentrations are lower with the 500 mg (b) (4) once-daily regimen compared to the 250 mg BID regimen. However, urine concentrations of ciprofloxacin following dosing with 500 mg CIPRO® XR are maintained well above (>100-fold) the *in vitro* MIC_{90} for *Escherichia coli* (about 0.03 µg/mL).

In vivo drug-drug interaction studies with CIPRO® XR were conducted with (b) (4) and omeprazole and submitted to this NDA. When ciprofloxacin (b) (4) was given 2 hours before or 4 hours after (b) (4) administration, there was an approximate 25% decrease in AUC. The mean decrease in C_{max} was 19% for administration of ciprofloxacin 4 hours after (b) (4), and 4% when ciprofloxacin was given 2 hours before (b) (4) The total amount of ciprofloxacin in urine, when CIPRO® XR was given with (b) (4) was not significantly different from when CIPRO® XR was given alone. Moreover, the urine concentrations of ciprofloxacin when (b) (4) was co-administered still exceeded the MIC_{90} for *E. coli* by at least 100-fold. Therefore, the applicant's proposal that CIPRO® XR can be given at least 2 hours before or 6 hours after antacid administration is acceptable. Concomitant administration of omeprazole with CIPRO® XR resulted in a 20% decrease in ciprofloxacin AUC and a 23% decrease in C_{max}. Similar to the situation with (b) (4) when omeprazole was co-administered, the total amount of ciprofloxacin excreted in urine was not significantly different from when CIPRO® XR was given alone, and the urine ciprofloxacin concentrations exceed the MIC_{90} for *E. coli* by at least 100-fold. Omeprazole and CIPRO® XR can be co-administered without dose adjustment.

Based on the efficacy results, the medical officer recommends approval for the CIPRO® XR tablets.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in original NDA 21-473 for CIPRO® XR. The Human Pharmacokinetics and Bioavailability Section of NDA 21-473 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. Specifications should be as follows:

30 minutes: (b) (4)
60 minutes: (b) (4)
120 minutes: (b) (4)

Labeling: The proposed label for ciprofloxacin (b) (4) tablets is attached.

Dakshina Chilukuri, Ph.D.
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Barbara Davit, Ph.D.
Briefing Day 12/10/02
cc: NDA 21-473, HFD-590, HFD-880 and CDR (Biopharm).

TABLE OF CONTENTS

SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Single-dose and steady-state pharmacokinetics of CIPRO 500 mg (b) (4) tablet vs. IR tablet

The applicant studied the single dose and steady state pharmacokinetics of a newly developed oral 500 mg ciprofloxacin once daily tablet 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 (250 mg immediate release given bid) was performed. The pharmacokinetic parameters determined were: maximum plasma concentration (C_{max}), maximum plasma concentration (C_{maxss}) 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}). The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new CIPRO 500 mg (b) (4) formulation to healthy male subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation.

Effect of food (pilot study) on pharmacokinetics of ciprofloxacin CIPRO 500 mg (b) (4) tablet

The applicant compared the safety, tolerability and pharmacokinetics the new CIPRO 500 mg (b) (4) formulation given after a standard breakfast (4 slices toast, 20g butter, 50g jam, 20g cheese, 200mL coffee (decaffeinated), 3g sugar) and after an overnight fast in comparison to the marketed ciprofloxacin product, given orally according to the bid dosing schedule as two doses of 250 mg to healthy subjects. After single dose administration of CIPRO 500 mg (b) (4) ciprofloxacin tablet to fasted healthy male subjects, the relative bioavailability (AUC_{0-24}) of ciprofloxacin was 94.8% and the 90% CI lay within the bioequivalence criteria compared with 250 mg bid IR standard tablet. However, C_{max} was significantly greater by 71.2% for the formulation compared to the 250 mg IR tablet. No effect of food on the exposure of ciprofloxacin was seen.

Effect of a high calorie, high fat meal on the pharmacokinetics of ciprofloxacin 500 mg (b) (4) tablet

The applicant evaluated the effect of a high calorie, high fat meal (250 mL whole milk, 2 slices toast, 2 scrambles 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 500 mg (b) (4) formulation in healthy subjects. The 500 mg Ciprofloxacin (b) (4) 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.

Effect of (b) (4) on the pharmacokinetics of ciprofloxacin 500 mg (b) (4) tablet

The applicant determined the influence of co-administration of the antacid (b) (4) on ciprofloxacin pharmacokinetics when a single 1000 mg dose of the ciprofloxacin MR

tablet was given 2 hours before or 4 hours after [redacted]. The ciprofloxacin AUC was decreased about 25% in both groups given [redacted], and this decrease was statistically significant. [redacted] did not effect the ciprofloxacin C_{max}. In both [redacted] groups, the amount of ciprofloxacin excreted into urine over 0-24 hours post-dosing was slightly decreased compared to ciprofloxacin given alone, but the differences were not statistically significant. In the groups receiving [redacted] urine ciprofloxacin concentrations were about 10 times greater than the highest observed *in vitro* MIC for most *E. coli* strains (1 µg/mL) throughout the 24-hour collection period after the ciprofloxacin dose. CIPRO® XR can be given at least 2 hours before or 6 hours after [redacted]

Effect of Omeprazole on the pharmacokinetics of ciprofloxacin 500 mg [redacted] tablet

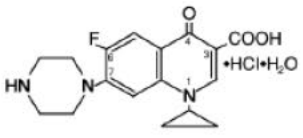
The applicant determined the influence of a three day 40 mg omeprazole pretreatment on the pharmacokinetics of ciprofloxacin administered orally as a 1000 mg dose of the ciprofloxacin [redacted] tablet 2 hours after a dose of 40 mg omeprazole. The exposure of ciprofloxacin was decreased (<20%) by pre-treatment with omeprazole compared with mono-treatment. However, the amount of ciprofloxacin excreted into urine 0-24 hours was not significantly changed following pre-treatment with omeprazole. In the omeprazole group, urine concentrations of ciprofloxacin throughout the 24-hour collection interval following dosing was over 10 times greater than the highest observed *in vitro* MIC for *E. coli*. CIPRO® XR can be co-administered with omeprazole without dose adjustment.

QUESTION BASED REVIEW

General Attributes

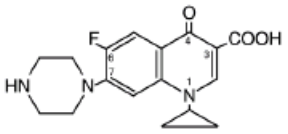
What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

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

(b) (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)	
Crospovidone	
Magnesium stearate	
Silica colloidal anhydrous	
CR -Layer	
Ciprofloxacin hydrochloride	
(b) (4)	
Succinic acid (b) (4)	
Hypromellose	
Magnesium stearate	
Silica colloidal anhydrous	
Film Coat	
Hypromellose	
Polyethylene glycol	
Titanium dioxide	
Total Weight	

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 uncomplicated urinary tract infections (acute cystitis), the recommended dosage of CIPRO® XR is 500 mg once daily for 3 days.

What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data?

The effectiveness of CIPRO® XR tablets (500 mg daily for 3 days) to treat uncomplicated UTI in adult women was compared with an accepted control agent for the treatment of acute uncomplicated UTI, the marketed Cipro tablets (250 mg BID for 3 days). In the pivotal phase III study that supports this NDA (Study 100346), the CIPRO® XR treatment regimen produced similar bacteriologic and clinical response rates as compared with the marketed Cipro 250 BID treatment regimen. In patients evaluated for efficacy, the bacteriologic eradication rate at test-of-cure (the primary efficacy assessment by a bacteriological method) was 94.5% in the Ciprofloxacin (b) (4) group and 93.7% in the Cipro 250 BID group. The 95% confidence interval for treatment difference in eradication rate (-3.5%, 5.1%) indicated that Ciprofloxacin (b) (4) 500 mg QD for 3 days was non-inferior to Cipro 250 BID for 3 days in the treatment of acute uncomplicated UTI in women. Similarity in eradication rates between the Ciprofloxacin (b) (4) group and the Cipro 250 BID group was consistent across centers and all demographic subgroups except age. Within the age categories, microbiologic success rate for the Ciprofloxacin (b) (4) group as compared to the control group was slightly lower among patients aged 18 to 44 years (93% vs. 96%, respectively), but higher among patients aged 44 to 65 (100% vs. 87%, respectively). Since no consistent trend with increasing age was found, this result could easily be due to random variation or the choice of cutoffs used for the age categories. Non- inferiority also was consistently demonstrated for the secondary variables (bacteriologic response at the late follow-up visit and clinical response at the test-of-cure and late follow-up visits) and for both analysis populations (valid for efficacy and valid for safety). The results of the pivotal study indicate that Ciprofloxacin (b) (4) given as a single 500 mg oral dose daily for 3 days, is effective treatment for acute uncomplicated urinary tract infections caused by susceptible microorganisms.

Table 8-4: Overall Clinical Success Rates: Clinical Cure at the Test-of Cure Visit (Day +4 to +11) and Continued Clinical Cure at the Late Follow-Up Visit (Day +25 to +50) – Valid for Efficacy Population

	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days	Cipro® 250 mg PO BID x 3 days	95% C.I. (Mantel-Haenszel)	95% C.I. (Normal Approximation)
Test-of-Cure Visit	189/198 (95.5%)	204/220 (92.7%)	-1.6%, 7.1%	-2.2%, 7.7%
Late Follow-Up Visit	161/181 (89.0%)	187/216 (86.6%)	-3.1%, 8.8%	-4.6%, 9.3%

See Study 100346, Table 14.2/12 (Test-of-Cure), and Table 14.2/14 (Late Follow-Up)

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Please refer to page 28 for a description of analytical methods and validation results.

What are the characteristics of the exposure-response relationships (for efficacy and safety?

The following table (Table 8-14) shows the urinary concentrations of ciprofloxacin after administration of (b) (4) and IR formulations in the pivotal (efficacy) study cure of acute uncomplicated urinary tract infections. Efficacy in the treatment of uncomplicated urinary tract infections depends upon antimicrobial concentrations in the urine rather than in the serum. Results of urinary concentrations of ciprofloxacin between 16 to 28 hours post dose in patients presenting with signs and symptoms of uncomplicated urinary tract infections enrolled in Study 100346 are summarized in Table 8-14 (below). The mean urinary concentration 20 to 24 hours after the last dose of ciprofloxacin (b) (4) 500 mg was 36.8 µg/mL, with a range of 3.6 to 177.2 µg/mL. There were fifteen valid-for-efficacy patients in the Ciprofloxacin (b) (4) group who had urinary concentrations of ciprofloxacin measured towards the end of the dosing interval (20 to 24 hours after the last dose of Ciprofloxacin (b) (4)). One of these 15 patients had persistence of the original causative organism *(E. coli*, MICs of 0.5 µg/mL and 1.0 µg/mL at the pre-therapy and test-of-cure visits, respectively) and another patient had a new infection *(E. faecalis*, MIC of 1.0 µg/mL). The clinical outcome for the patient with bacterial persistence was a cure, but that for the patient with a new infection was a failure. The urinary concentrations of ciprofloxacin for these 2 patients were 11.0 µg/mL and 38.7 µg/mL, respectively. Thus, the lack of clinical and/or microbiologic success in these two patients was not due to low urinary concentration of ciprofloxacin. The lowest observed urinary concentration at any time in any individual patient who received Ciprofloxacin (b) (4) was 3.3 µg/mL, which is more than 100 times the MIC_{90} for *E. coli*.

Table 8-14: Mean (± SD) Urinary Concentrations (µg/mL) of Ciprofloxacin After Administration of Ciprofloxacin (b) (4) 500 mg QD Versus Immediate-Release Ciprofloxacin 250 mg BID in Patients with Uncomplicated Urinary Tract Infections (Study 100346)

	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days		Cipro® 250 mg PO BID x 3 days	
	Number of Patients	**Mean Urinary Concentration ± SD**	**Number of Patients**	**Mean Urinary Concentration ± SD**
Collection Interval[a]				
16-20 Hours Post Dose	5	65 ± 45	3	28 ± 6
20-24 Hours Post Dose	24	37 ± 37	21	65 ± 76
24-28 Hours Post Dose	3	21 ± 12	3	49 ± 33

a For the Cipro® 250 mg BID regimen, time is referenced to the first dose of a 24-hour cycle.
See Study 100346, Table 14.4/1

Urinary concentrations of ciprofloxacin following the new 500 mg QD formulation compared with the 250 mg immediate-release formulation given bid are presented in the following table (8-13), which is taken from clinical pharmacology study 10325. The

amount of ciprofloxacin excreted unchanged in urine was similar after administration of Ciprofloxacin (b) (4) and the corresponding immediate- release ciprofloxacin treatment given twice daily. Higher urinary ciprofloxacin concentrations were reached for Ciprofloxacin (b) (4) in the period up to 12 hours post-dose as compared to the corresponding immediate- release formulation. It is not clear if this is related to a potentially improved urinary bactericidal activity within this time frame. Urinary concentrations of ciprofloxacin remained above the MIC values for susceptible organisms typically found in the urine of patients with uncomplicated urinary tract infections throughout the dosing interval. Even in the post-treatment sample collected 24 to 28 hours after the last dose of Ciprofloxacin (b) (4), the mean urinary concentration was 11 µg/mL (range of 3.3 µg/mL to 33.2 µg/mL).

Table 8-13: Mean (± SD) Urinary Concentrations (µg/mL) of Ciprofloxacin After Administration of Ciprofloxacin (b) (4) 500 mg QD Versus Immediate-Release Ciprofloxacin 250 mg BID in Healthy Volunteers (Clinical Pharmacology Study 10325, N = 16)

	0-4 Hours	4-8 Hours	8-12 Hours	12-24 Hours	24-28 Hours
Day 1 Ciprofloxacin (b)	338 ±244	137 ± 75	57 ± 48	27 ± 14	
Day 1 Ciprofloxacin IR[a]	161 ± 79	65 ± 38	27 ± 17	123 ± 50	
Day 5 Ciprofloxacin (b) (4)	368 ± 267	166 ± 90	53 ± 40	30 ± 19	11 ± 8
Day 5 Ciprofloxacin IR	196 ± 94	82 ± 51	31 ± 22	128 ± 50	29 ± 12

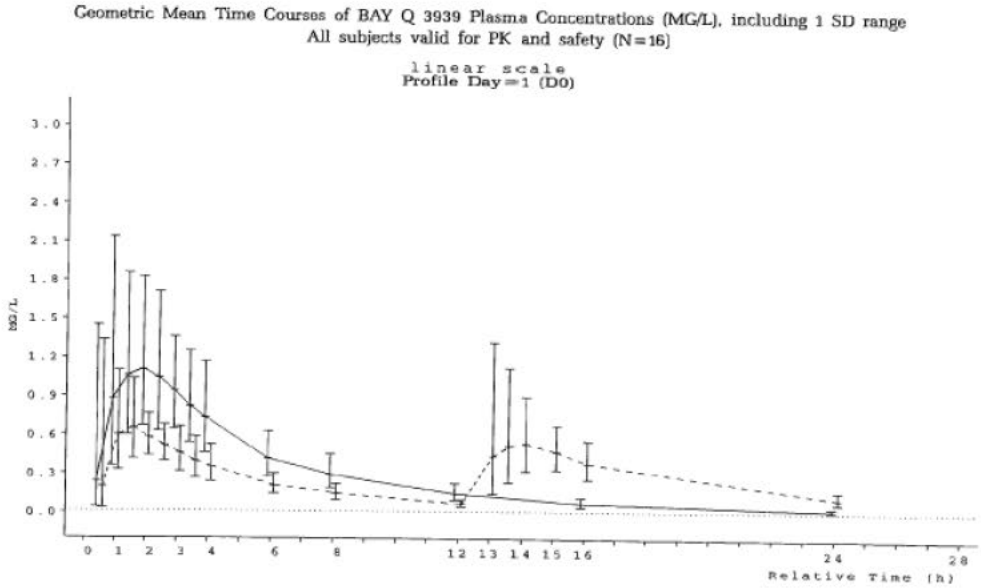
a IR = Immediate-release ciprofloxacin; collection times for this formulation (given BID) are referenced to the first dose of a 24-hour cycle.

See Study 10325

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 (b) (4) 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 4.61 for the CIPRO® XR formulation and was 3.01 for the IR formulation. The presence of an IR component in the CIPRO® XR product may be the cause for higher ratio.



Note: Solid line = 500 mg BAY q 3939 od, dashed line = 250 mg BAY q 3939 bid
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.

How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The following table shows the plasma concentrations (trough values) measured in patients enrolled in the pivotal study (Study 100346). The mean trough plasma concentration of ciprofloxacin for CIPRO® XR formulation was somewhat lower (0.13 mg/L) than the concentration for conventional Cipro IR formulation (0.20 mg/L). However, urine samples collected at the end of the dosing interval demonstrated maintenance of adequate ciprofloxacin concentrations to treat uncomplicated UTI. The mean urine concentration of ciprofloxacin in patients taking CIPRO® XR 500 mg daily was 37 mg/L, slightly lower than the value of 65 mg/L observed for patients taking Cipro 250 mg BID. Although there was considerable variability in urine concentrations, the lowest ciprofloxacin concentration observed after administration of the Ciprofloxacin (b) (4) formulation at any time was 3.6 mg/L, well in excess of the MIC_{90} of 0.03 mg/L reported for *E. coli*.

Table 11-9: Trough plasma and urine concentrations (mg/L) of ciprofloxacin following Ciprofloxacin (b) (4) 500 mg or Cipro® 250 mg BID

	Ciprofloxacin (b) (4) 500 mg QD			Ciprofloxacin 250 mg BID		
	N	Mean	Range	N	Mean	Range
Plasma concentration (mg/L)	23	0.13	0-1.6	22	0.20	0-0.6
Urine concentration (mg/L)	24	37	3.6-177.2	21	65	6.6-308.8

What are the basic PK parameters?

The PK parameters in healthy volunteers are given below:

Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO® and CIPRO® (b) (4) Administration

	C_{max} (mg/L)	AUC_{0-24h} (mg•h/L)	$T_{1/2}$ (hr)	T_{max} (hr)§
CIPRO (b) (4) 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)

§ median (range)

What is the inter-individual variability of PK parameters in subjects?

The interindividual variability of the pharmacokinetic parameters was low (<30%) as known for ciprofloxacin and appeared comparable between the treatments.

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

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) 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.

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 mild to moderate renal impairment. The package insert for Cipro® (b) (4) tablets states that a dose adjustment is necessary only for patients with severe renal dysfunction (creatinine clearance = 29 mL/min), and for patients on hemodialysis or peritoneal dialysis. No dose adjustment is proposed for patients with renal impairment. There are several assumptions underlying this proposal:

1. Ciprofloxacin is eliminated by both renal and hepatic routes. The hepatic pathway appears to compensate to an extent in reduced renal function.
2. The original CIPRO ((b) (4) tablet) NDA contained a study of the effects of renal impairment on ciprofloxacin PK. Only in severe renal impairment was there a clinically significant decrease in ciprofloxacin clearance, necessitating a dose adjustment. In severe renal impairment (Clcr < 30 mL/min), ciprofloxacin plasma concentrations (AUC) were about 2.5x values in subjects with normal renal function.
3. Assuming that the plasma concentrations will also increase by 2.5x in renally impaired patients given CIPRO XR, the AUC_{24} would likely increase from about 8 to about 20 µg*hr/mL.

4. The highest recommended dosing regimen for the CIPRO [redacted] tablet is 750 mg bid for up to 14 days. This regimen gives an AUC_{24} of about 32 µg*hr/mL.
5. The label for the CIPRO [redacted] tablet recommends dose adjustments for patients who are severely renally impaired. Doses should not exceed 500 mg, and the dosing interval is increased to 18 hours for patients severe renal impairment, and to 24 hours in dialysis patients.
6. For UTI, proposed treatment with CIPRO XR is 500 mg once daily for 3 days. This is the same as the maximum dose recommended for severely renally impaired subjects. Moreover, the daily exposure anticipated in patients with severe renal impairment receiving 500 mg once daily should be well below that observed at the 750 mg bid dosing regimen.

The package insert for Cipro® [redacted] tablets states that in studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The package insert also states that the kinetics of ciprofloxacin in patients with acute hepatic insufficiency have not been fully elucidated. No dose adjustment of Cipro® [redacted] tablets is recommended for patients with hepatic impairment. Therefore, no dose adjustment is recommended for patients with hepatic impairment taking CIPRO® XR tablets.

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.

b) pediatric patients

Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals.

c) gender

N/A

d) race

The majority of patients in the pivotal Phase III study were White (79%). Eight percent of the study population were Black and 10% were Hispanic. There was no trend overall for microbiologic success by race for both treatment groups (Table 8-9). No special labeling regarding response by race appears necessary for Ciprofloxacin [redacted]

Table 8-9: Overall Microbiologic Success at the Test-of-Cure Visit (Day +4 to +11) by Race – Valid for Efficacy Population

	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days N = 199		Cipro® 250 mg PO BID x 3 days N = 223	
	N/n	**%**	**n/n**	**%**
All Patients	188/199	94.5	209/223	93.7
White	146/154	94.8	166/179	92.7
Black	17/17	100.0	18/18	100.0
Hispanic	18/21	85.7	19/20	95.0
Other	7/7	100.0	6/6	100.0

See Study 100346, Table 14.2/4

e) renal impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. The package insert for Cipro® (b) (4) tablets states that a dose adjustment is necessary only for patients with severe renal dysfunction (creatinine clearance = 29 mL/min), and for patients on hemodialysis or peritoneal dialysis. No dosage adjustments are needed for patients with severe renal dysfunction and the proposed labeling will indicate that CIPRO® XR may be administered to patients with severe renal dysfunction without any dosage adjustment.

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 (b) (4) 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?

(b) (4)

It is known that co-administration of aluminum and magnesium based antacids, such as (b) (4), significantly impair the absorption of ciprofloxacin, as well as other quinolones. The mechanism of this interaction is the formation of non- absorbable chelate complexes between the quinolone and the metal cations of the antacid product. Current labeling for (b) (4) ciprofloxacin recommends withholding ciprofloxacin until at least 6 hours after administration of (b) (4) and withholding (b) until at least 2 hours after administration of ciprofloxacin. In order to determine if these dose-time restrictions could be altered with the (b) (4) tablet, a study was performed in healthy male subjects comparing the pharmacokinetics of the (b) (4) tablet given alone, 4 hours after 10 mL (b) (4), and 2 hours before (b) (4) The details of the study design and results are given below:

Objectives: The primary objective of the study was to evaluate the influence of the co-administration of the antacid (b) (4) given 2 h after or 4 h before the administration of a 1000 mg Cipro (b) (4) tablet on the pharmacokinetics of ciprofloxacin

Study design: This was a single center, randomized, non-blinded, three-fold crossover design in 18 healthy male subjects. The following treatments were administered:

- **Treatment A**: Single dose administration of 1000 mg Ciprofloxacin (b) (4) after an overnight fast.
- **Treatment B**: Single dose administration of 1000 mg Ciprofloxacin (b) (4) **four hours after** treatment with 10mL (b) (4) suspension after an overnight fast.
- **Treatment C**: Single dose administration of 1000 mg Ciprofloxacin (b) (4) **two hours before** treatment with 10mL (b) (4) suspension after an overnight fast

The treatments were separated by a washout period of at least one week.

Results:
The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized below. Also presented are the 90% confidence intervals for the test/reference ratios.

PK parameters of ciprofloxacin after administration of the dose 2 h before a single dose of (b) (4) in comparison to the mono-treatment (N=15)

PK parameter*	Mono-treatment (N=15)	Combination-treatment (N=15)
C_{max} (mg/mL)	2.74 (1.35)	2.78 (1.35)
AUC_{inf} (mg-h/mL)	15.5 (1.33)	12.5 (1.29)
T_{max} (h)#	1.5 (0.5-3.0)	2.0 (1-2)
Ae_{ur} (mg)	31.2 (8.53)	24.6 (6.68)
$T_{1/2}$ (h)	5.61 (1.17)	4.70 (1.12)

*Parameters are presented as geometric means (geometric SD)
#Values are medians for tmax

Figure: Plasma concentration vs. time profiles of ciprofloxacin following administration of the 1G [redacted] tablet with and without staggered dosing with [redacted] 70 (geometric mean, N=15, circles: reference treatment, squares: ciprofloxacin 2h before [redacted] 70, triangles: ciprofloxacin 4h after [redacted])

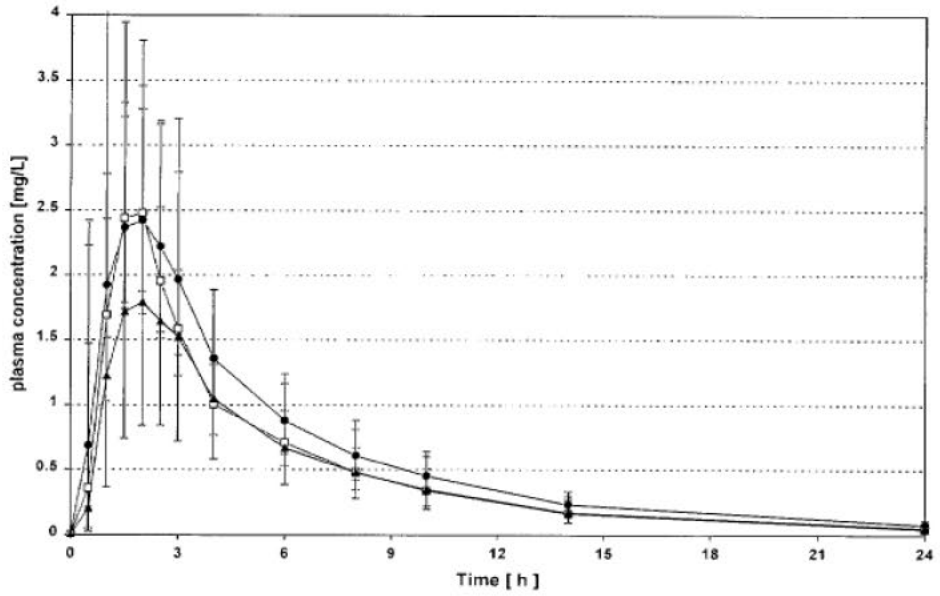
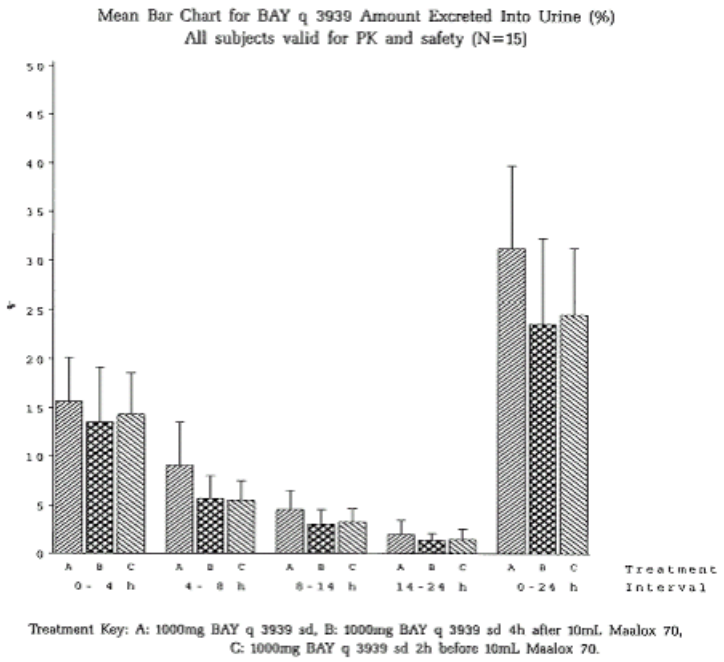


Table 11.5.4-1: Mean ratios and 90% confidence intervals for primary parameters AUC and C_{max} of ciprofloxacin

Population	Para-meter	Comparison	Mean ratio Combi / Mono	90% confidence interval	Within-Subject CV (%)
PK and safety, N=15	AUC	B : A	0.74	(0.58, 0.95)	41.1
		C : A	0.76	(0.59, 0.98)	
	C_{max}	B : A	0.81	(0.61, 1.07)	47.9
		C : A	0.96	(0.72, 1.28)	
PK and safety, (Subject 16 excluded), N=14	AUC	B : A	0.88	(0.77, 1.00)	20.4
		C : A	0.81	(0.71, 0.93)	
	C_{max}	B : A	0.97	(0.82, 1.15)	26.6
		C : A	1.03	(0.86, 1.22)	

Treatment Key: A: 1000mg BAY q 3939 s.d., B: 1000mg BAY q 3939 s.d. given 4 h after 10mL [redacted] 70, C: 1000mg BAY q 3939 s.d. given 2 h before 10mL [redacted] 0.

Note: Subject 16 was excluded by the applicant since the Cmax and AUC values were significantly lower than the other subjects in the group. However, the study review rejected the applicant's claim and the conclusions were obtained using data from all subjects.

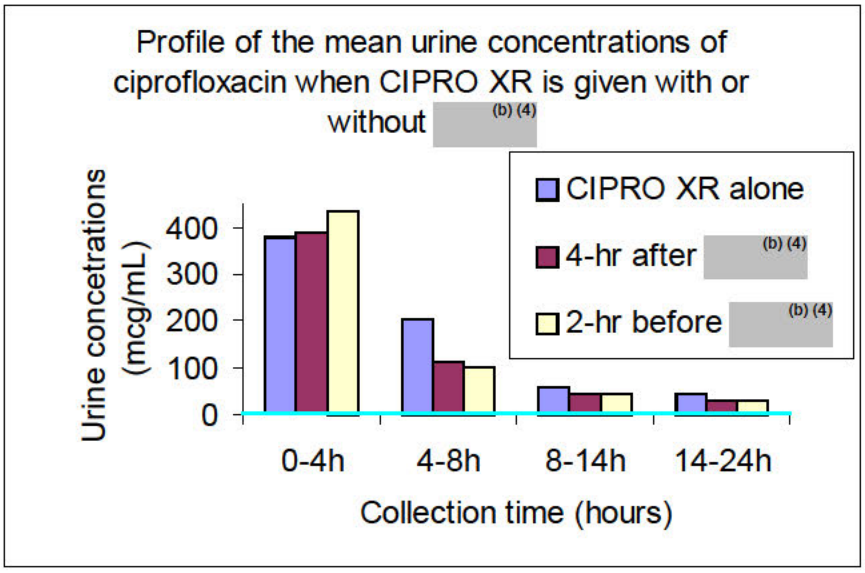


The applicant proposes that the CIPRO® XR label should recommend that CIPRO® XR be administered either 6 hours after, or 2 hours before antacid products. To determine if this is feasible, ciprofloxacin urine concentrations in this study were compared to *in vitro* minimum effective concentrations (MIC_{90}) values for *E. coli*, the main organism responsible for uncomplicated urinary tract infections.

Urine ciprofloxacin concentrations (µg/mL) when CIPRO® XR was given with or without (b)(4)

Collection time (h)	CIPRO® XR alone	4 hr after (b)(4)	2 hr before (b)(4)
0-4	161 - 764 (mean = 377)	43 - 1134 (mean = 387)	165 -1154 (mean = 434)
4-8	35 - 528 (mean = 203)	24 - 291 (mean = 112)	31 - 290 mean = 103)
8 - 14	13 - 103 (mean = 58)	4.9 - 86 (mean = 43)	18 - 97 (mean = 46)
14-24	12 - 73 (mean = 44)	9.6 - 67 (mean = 32)	9.6 - 52 (mean = 30)

A plot showing the urinary concentrations (µg/mL) when CIPRO® XR was given with or without Maalox is shown below. The MIC_{90} for *E.coli* is also represented in the plot.



The MIC_{90} values for most *E. coli* (the main UTI organism) are usually about 0.03 µg/mL. Some may be somewhat higher but most are below the susceptible breakpoint of 1 µg/mL. Therefore, although ciprofloxacin urine concentrations were reduced when co-administered with antacids, these concentrations remained well above the MICs for the organisms of interest throughout the 24-hour dosing interval.

As shown above, the rate of ciprofloxacin absorption was not affected by (b) (4). The extent of systemic absorption (AUC) was reduced by about 26% after co-administration of (b) (4) 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 (b) (4), 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 (b) (4) is administered.

Omeprazole:

Alteration of gastric pH may influence the absorption of certain compounds by changing solubility or stability. For immediate release ciprofloxacin, no interaction was observed with concomitant administration of cimetidine or ranitidine, H2 antagonists, which elevate gastric pH. However, a slight reduction in ciprofloxacin bioavailability was reported when ciprofloxacin was given along with the proton pump inhibitor omeprazole. A randomized, two-period crossover study was performed to determine the potential for an interaction between ciprofloxacin (b) (4) and omeprazole. The details of the study design and results are given below:

Objectives: The primary objective of the study was to evaluate the influence of a three day 40 mg omeprazole pretreatment on the pharmacokinetics of ciprofloxacin administered orally as a 1000 mg Cipro (b) (4) tablet 2 hours after a dose of 40 mg omeprazole.

Study design: This was a single center, randomized, non-blinded, two-fold crossover design in 18 healthy male subjects. The treatments were separated by a washout period of at least one week. The following treatments were administered:

- **Treatment A**: Single dose administration of 1000 mg Ciprofloxacin (b) (4) after an overnight fast.
- **Treatment B**: Single dose administration of 1000 mg Ciprofloxacin (b) (4) following pretreatment for three days with 40 mg omeprazole once daily after an overnight fast and 2 hours after the morning dose of omeprazole

Results: The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized below. Also presented are the 90% confidence intervals for the test/reference ratios.

PK parameters of ciprofloxacin

PK parameter*	Mono-treatment (N=17)	Combination-treatment (N=17)
C_{max} (mg/mL)	2.70 (1.28)	2.08 (1.58)
AUC_{inf} (mg-h/mL)	14.9 (1.23)	12.0 (1.45)
T_{max} (h)#	2.5 (1-4)	2.5 (1-4)
Ae_{ur} (%)	31.1 (7.22)	25.5 (8.37)
$T_{1/2}$ (h)	5.45 (1.15)	5.45 (1.13)

*Parameters are presented as geometric means (geometric SD)
#Values are medians for t_{max}

Figure 11.5.2-1: Plasma concentration vs. time profiles of ciprofloxacin given as 1000 mg (b) (4) tablet to healthy subjects with (dotted line) and without (straight line) 3 day 40 mg once daily omeprazole pretreatment (geo. mean, N=17)

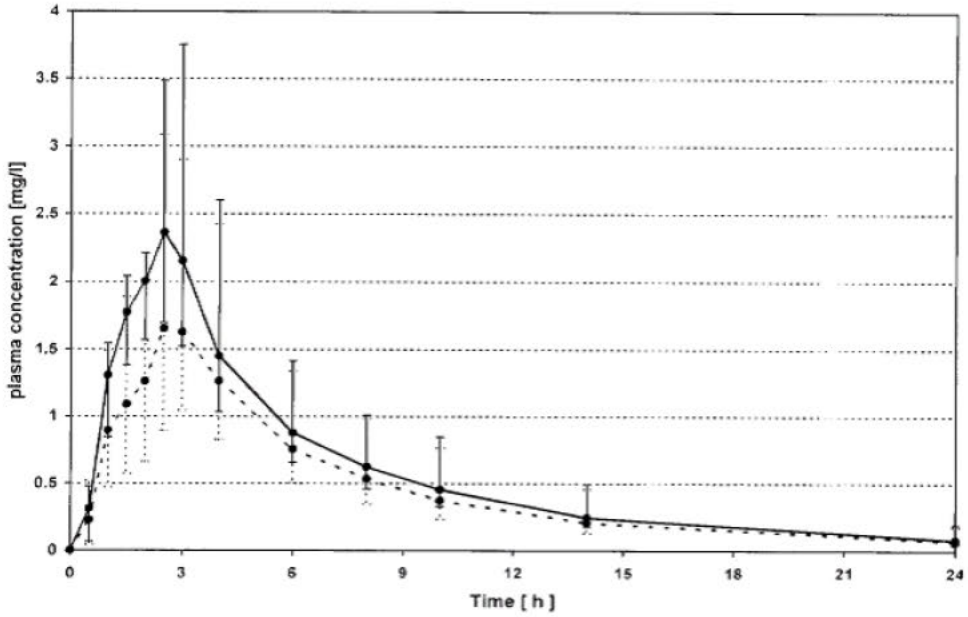
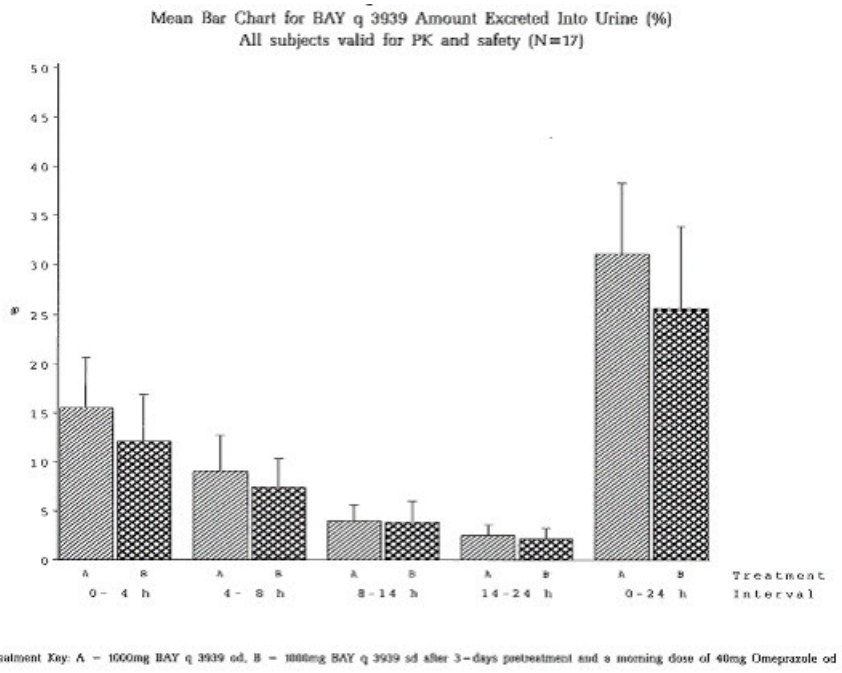


Table 3-1: Pharmacokinetics of ciprofloxacin following administration of 1000 mg alone or with omeprazole (40 mg/day)

	Ciprofloxacin alone (A)	Ciprofloxacin + Omeprazole (B)	Ratio (B/A) (90% CI)
AUC (mg*h/L)	14.9 (21%)	12.0 (37%)	0.80 (0.69-0.93)
C_{max} (mg/L)	2.7 (25%)	2.1 (46%)	0.77 (0.63-0.94)
t_{max} (hr)*	2.5 (1-4)	2.5 (1-4)	-

*median (range)



In the urine, slightly decreased ciprofloxacin concentrations were observed for the combination treatments for the interval compared with the mono-treatment.

Urine ciprofloxacin concentrations (µg/mL) when CIPRO® XR was given with or without omeprazole

Collection time post-dosing	CIPRO® XR alone	CIPRO® XR + omeprazole
0-4 hours	120 - 907 (mean = 382)	38 - 1736 (mean = 460)
4-8 hours	50 - 449 (mean = 169)	45 - 529 (mean = 144)
8-14 hours	22 - 147 (mean = 70)	14 - 203 (mean = 68)
14-24 hours	14 - 93 (mean = 47)	10 - 106 (mean = 47)

As previously stated, the MICs for most *E. coli* strains are about 0.03 µg/mL. Although urine ciprofloxacin concentrations are reduced somewhat with omeprazole co-administration, values still exceed the MIC by greater than 100-fold.

As shown above, omeprazole slightly reduced the rate and extent of ciprofloxacin exposure. The exposure of ciprofloxacin is decreased (20%) by pre-treatment with omeprazole compared with mono-treatment. 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 the drug from the dosage form?

The effects of food on the pharmacokinetics of ciprofloxacin following administration of a single dose of the 500 mg (b) (4) formulation was investigated in a two-way crossover study. Subjects received study drug either after an overnight fast or a high-fat breakfast. As shown in the table below, ciprofloxacin pharmacokinetics are not altered by co-administration with food.

PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles

PK parameter*	500 mg (b) (4) fasted (N=20)	500 mg (b) (4) fed (N=20)
C_{max} (mg/mL)	1.34 (1.52)	1.30 (1.30)
AUC_{0-24} (mg-h/mL)	6.79 (1.43)	6.82 (1.22)
AUC_{inf} (mg-h/mL)	7.05 (1.43)	7.12 (1.23)
T_{max} (h)#	1.5 (0.5-3.5)	3.5 (1.5-4.0)
$T_{1/2}$ (h)	5.59 (1.11)	5.55 (1.09)
Ae_{ur} (%)	34.3	33.5

*Parameters are presented as geometric means (geometric SD)
#Values are medians for tmax

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 dissolution testing conditions:

Apparatus:	USP Apparatus II (Paddle)
Dissolution medium:	900 mL 0.1N HCl
Bath temperature:	37 ± 0.5 °C
Rotation speed:	50 rpm
Specifications:	30 minutes: (b) (4)
	60 minutes: (b) (4)
	120 minutes: (b) (4)

In the following tables and figures, the dissolution data and profiles of ciprofloxacin (b) (4) tablets at various dissolution conditions are presented. The applicant tested dissolution in 0.1 N HCl, 0.1 N HCl + NaCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water. The applicant also tested the effect of agitation rate on the dissolution profile.

2.3.1 Influence of Dissolution Medium

Ciprofloxacin (b) (4) Tabl 0.5G Coat **815**, batch no 529524H (K-V/7), 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**	25.3
30													**42**	10.4
45													**54**	7.2
60													**62**	7.0
90													**75**	6.5
120													**85**	5.3
180													**96**	2.5
240													**100**	1.6
300													**100**	1.5
360													**100**	1.5

Ciprofloxacin (b) (4) Tabl 0.5G Coat **815**, batch no 529524H (ME/S-X/1), diss medium: **0.01N HCl + NaCl**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**33**	14.9
30							**47**	6.2
45							**57**	5.6
60							**65**	5.9
90							**78**	5.8
120							**87**	4.8
180							**97**	1.5
240							**100**	0.8
300							**100**	0.8
360							**100**	0.9

Ciprofloxacin (b) (4) Tabl 0.5G Coat **815**, batch no 529524H (ME/S-IX/1), diss. medium: **acetate buffer pH4.5**

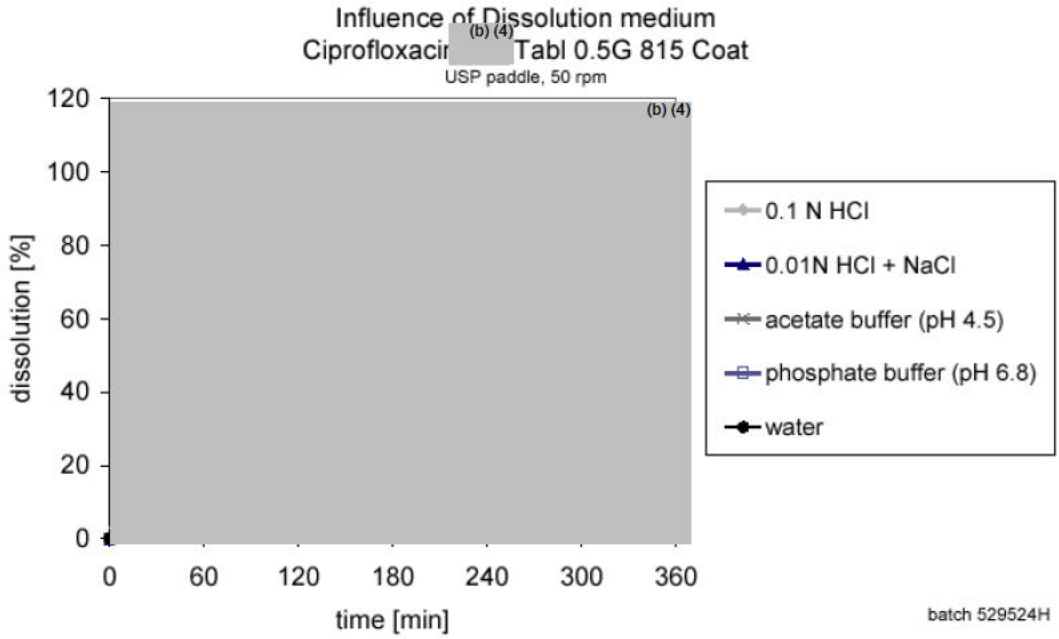
sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**35**	10.9
30							**50**	5.0
45							**58**	4.4
60							**66**	4.4
90							**77**	3.6
120							**86**	2.7
180							**97**	1.2
240							**99**	0.6
300							**99**	0.7
360							**99**	0.7

Ciprofloxacin (b) (4) Tabl 0.5G Coat **815**, batch no 529524H (ME/S-VIII/15), dissolution medium: **water**

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	**Average [%]**	COV [%]
15 [min]	(b) (4)						**27**	8.2
30							**44**	4.1
45							**53**	2.6
60							**60**	2.5
90							**71**	2.8
120							**80**	2.8
180							**91**	1.9
240							**96**	1.4
300							**97**	1.3
360							**97**	1.4

Ciprofloxacin (b) (4) Tabl 0.5G Coat **815**, batch no 529524H (ME/S-IX/5),
dissolution 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)						**2**	10.7
30							**4**	13.3
45							**5**	11.7
60							**5**	9.5
90							**6**	7.8
120							**7**	7.1
180							**8**	6.9
240							**9**	6.7
300							**10**	6.5
							10	6.4



2.3.2 Influence of agitation

Ciprofloxacin [redacted] Tabl 0.5G Coat **815**, batch no 529524H (K-V/7) 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]	[redacted]						**24**	17.3
30							**43**	7.0
45							**54**	4.4
60							**62**	4.7
90							**75**	4.5
120							**85**	3.4
180							**97**	1.9
240							**101**	1.3
300							**100**	1.3
360							**101**	1.4

Ciprofloxacin [redacted] Tabl 0.5G Coat **815**, batch no 529524H (ME/S-IX/16) 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]	[redacted]						**39**	8.0
30							**54**	4.6
45							**65**	5.1
60							**74**	5.0
90							**87**	4.4
120							**95**	2.9
180							**99**	1.9
240							**99**	1.9
300							**99**	1.9
360							**99**	1.9

[redacted]

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 ciprofloxacin 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 on (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

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/s/

Dakshina Chilukuri
12/16/02 08:49:59 AM
BIOPHARMACEUTICS

Barbara Davit
12/16/02 11:19:47 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	21-473	**Sponsor:**	Bayer Corporation
IND:	61,331		
Brand Name:	Cipro® (b) (4)	**Priority Classification:**	Standard
Generic Name:	Ciprofloxacin hydrochloride and Ciprofloxacin* Tablets * Does not comply with USP.	**Indication(s):**	Uncomplicated Urinary Tract Infection (UTI)
Drug Class:	Fluoroquinolone antibiotic	**Date of Submission:**	March 4, 2002
Dosage Form:	(b) (4) tablet	**Route of Admin.:**	Oral
Dosing Regimen:	500 mg po QD x 3 days	**Due Date of Review:**	December 2002
Division:	DPE III (HFD-880)	**Medical Division:**	DSPIDP (HFD-590)
Reviewer:	Joette Meyer, Pharm.D.	**Team Leader:**	Barbara Davit, Ph.D.

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	x		
Tabular Listing of All Human Studies	x		
HPK Summary	x		
Labeling	x		
Reference (b) (4) and Analytical Methods	x		
Bioavailability and Bioequivalence Studies	x		
Mass Balance Study		x	
BA Studies	x		
Absolute BA		x	
Relative BA	x		
BE Studies		x	
Average BE		x	
Population BE		x	
Individual BE	x		
Food-Drug Interaction	x		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)	x		

Studies Using Human Biomaterials			
Plasma Protein Binding Studies		x	
Blood/Plasma Ratio		x	
Metabolism Studies Using Hepatocytes, Microsomes,etc		x	
In Vitro Drug Interaction Studies		x	
Human Pharmacokinetics Studies	x		
PK, and Initial Safety and Tolerability in Healthy Volunteers	x		
Single Dose	x		
Multiple Dose	x		
PK, and Initial Safety and Tolerability in Patient Volunteers		x	
Single Dose			
Multiple Dose			
Dose Proportionality		x	
Single Dose			
Multiple Dose			
PK in Population Subsets to Evaluate Effects of Intrinsic Factors		x	
Ethnicity		x	
Gender		x	
Pediatrics		x	
Geriatrics		x	
Renal Impairment		x	
Hepatic Impairment		x	
PK to Evaluate Effects of Extrinsic Factors	x		
Drug-Drug Interaction: Effects on Primary Drug	x		
Drug-Drug Interaction: Effects of Primary Drug		x	
Population PK studies		x	
Summary Table of PK/PD Studies		x	
PK/PD studies in Volunteers		x	
PK/PD studies in patients		x	
Individual Datasets for all PK and PK/PD studies in electronic format		x	
Other		x	
Genotype/Phenotype Studies			
Chronopharmacokinetics			

This application is__X__is not___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)

How does the bioavailability, in terms of C_{max}, AUC, and C_{min} compare between [redacted] (b) (4) [redacted] (b) (4) ciprofloxacin and [redacted] (b) (4) ciprofloxacin?

How do urinary concentration of ciprofloxacin obtained with the [redacted] (b) (4) compare to the [redacted] (b) (4)?

What effect does the administration of food, antacids, and omeprazole have on the absorption of ciprofloxacin from the [redacted] (b) (4) tablet?

Requests/Comments are __X_ are not __ to be sent to firm. If any was sent, indicate the date of FDA letter.

Please submit the raw data and dissolution profiles for the three test batches of tablets. If this information has already been submitted, please indicate where it may be found in the submission.

Signature _____ _____

Primary Reviewer **Team Leader/Secondary Reviewer**

cc:
HFD-590: /NDA 21-473
/PM/SalibaJ
HFD-880: /BiopharmTL/DavitB
/Biopharm/MeyerJ

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/s/

Joette Meyer
4/18/02 04:31:22 PM
BIOPHARMACEUTICS

Barbara Davit
4/19/02 11:54:10 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDAs #: 21-473

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 04-MAR-02
CDER DATE: 04-MAR-02
REVIEW ASSIGN DATE: 07-MAR-02
REVIEW COMPLETE DATE: 17-MAY-02

SPONSOR:
Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON:
Andrew S. Verderame
Deputy Director, Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Original New Drug Application (CIPRO® (b) (4)

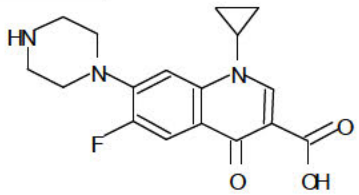
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Uncomplicated Urinary Tract Infections

DOSAGE FORM: 500-mg Tablets

DRUG PRODUCT NAME

PROPRIETARY: CIPRO® (b) (4)
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: (b) (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

BACKGROUND:

This application is for a new tablet formulation of ciprofloxacin. This new formulation is a once daily (b) (4) tablet. These ciprofloxacin (b) (4) 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 (b) (4) 500 mg tablets compared to Cipro® 250 mg twice daily).

This application is for the indication of uncomplicated urinary tract infections. One randomized, double-blind, controlled multicenter clinical trial (Study 100346) forms the basis of the clinical section of the application. This trial was performed in patients with uncomplicated urinary tract infections and enrolled 250 patients. This trial compared ciprofloxacin (b) (4) 500 mg tablets given once a day for 3 days with Cipro® 250 mg tablets given twice a day for 3 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 14-17.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The applicant is requesting an indication of uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli,* (b) (4) *Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus.*

From the microbiology viewpoint this application should be approved with minor changes needed in the microbiology section of the label.

In Study 100346 CIPRO (b) (4) tablets (500 mg once daily for 3 days) were compared with immediate-release ciprofloxacin tablets (250 mg twice daily for 3 days) in the treatment of uncomplicated urinary tract infections. The trial enrolled 905 patients. The primary endpoint was bacteriological eradication at 4-11 days post-therapy. The bacteriological eradication rate for CIPRO (b) (4) tablets was 94.5% (188/199) compared to 93.7% (209/223) 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 (b) (4) (500 mg QD)	Cipro Immediate Release (250 mg BID)
Escherichia coli	156/160 (97.5%)	176/181 (97.2%)
Enterococcus faecalis	10/11 (90.9%)	17/21 (81.0%)
Klebsiella pneumoniae	7/9 (77.8%)	11/14 (78.6%)
Proteus mirabilis	11/12 (91.7%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83.3%)	7/7 (100%)

As usual in uncomplicated 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 five of the listed pathogens.

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

No new information has been submitted.

IN VITRO ACTIVITY AGAINST RECENT CLINICAL ISOLATES FROM UTIs

SURVEILLANCE STUDIES

A surveillance study of the four most commonly isolated UTI pathogens was conducted during October-December 1999 (1). The organisms were collected from urine cultures regardless of the patients' age, gender, or inpatient/outpatient status. MIC data was collected for several antibiotics including ciprofloxacin. The results are shown in TABLE 1.

TABLE 1
Ciprofloxacin MIC Data for UTI Isolates (10/99-12/99)

Organism	Total Number	Modal MIC (μg/mL)	MIC_{90} (μg/mL)	% Resistant
Escherichia coli	5883	0.015	0.03	3.2
Klebsiella pneumoniae	1777	0.03	0.25	3.7
Proteus mirabilis	1888	0.03	4	10.8
Staphylococcus saprophyticus	613	0.25	0.5	0.3

The MIC_{90} was less than 1.0 μg/mL for all the tested pathogens, except *Proteus mirabilis*. The modal MIC was only 0.03 μg/mL for *Proteus mirabilis* and only slightly more than 10% were resistant. Most isolates of *Proteus mirabilis* were, therefore, susceptible to ciprofloxacin. *Enterococcus faecalis* was not studied. This is the UTI organism that is most resistant to ciprofloxacin. It is approved for UTI in the present ciprofloxacin (b) (4) tablet labeling.

The (b) (4) (b) (4) provided national surveillance data for UTI isolates for the year 2000. More than 175 medical centers contributed to this database. TABLE 2 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
Escherichia coli	151,668	95.9	0.1	4.0
Klebsiella pneumoniae	26,040	95.4	0.6	4.0
Proteus mirabilis	15,764	86	1.2	12.9
Staphylococcus saprophyticus	1,139	98.6	0	1.4
Enterococcus faecalis	13,772	66.2	4.5	29.3

These data for the year 2000 are similar to those in the previous study for the end of 1999. Once again about 10% of *Proteus mirabilis* were resistant to ciprofloxacin. Almost 30% of *Enterococcus faecalis* isolates were resistant to ciprofloxacin. *Enterococcus faecalis* is approved for 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. (b) (4) is proposed for the labeling of this product.

DATA FROM THE CLINICAL STUDY

This application has one pivotal study 100346. This was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter study conducted in the United States in adult female patients with uncomplicated urinary tract infections. The main objective of the study was to compare the safety and efficacy of Ciprofloxacin (b) (4) 500 mg oral tablets given once daily for 3 days with conventional, immediate-release ciprofloxacin tablets 250 mg given twice a day for 3 days. The primary efficacy was microbiological outcome at the test-of-cure visit (4 to 11 days post-treatment). Secondary efficacy parameters were microbiological outcome at the late follow-up visit (Day 25 to 50) 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 from the Ciprofloxacin (b) (4) arm are listed in TABLE 3. *Escherichia coli* was the most frequently isolated organism (n=160), followed by *Proteus mirabilis* (n=12) and *Enterococcus faecalis* (n=11). The MIC_{90} for *E. coli* was 0.03 μg/mL, which is the same as for isolates of *E. coli* in the surveillance studies.

TABLE 3
MICs of Pre- therapy Isolates in Ciprofloxacin (b) (4) Arm

Organism	Total Number	Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Escherichia coli	160	0.008-16	0.015	0.03
Klebsiella pneumoniae	9	0.015-0.06	0.06	0.06
Proteus mirabilis	12	0.015-0.03	0.03	0.03
Proteus vulgaris	1	0.03	----	----
Enterobacter cloacae	2	0.008-0.015	----	----
Enterobacter aerogenes	2	0.03-0.06	----	----
Stenotrophomonas maltophilia	1	0.015	----	----
Enterococcus faecalis	11	0.5-2	1	1
Staphylococcus saprophyticus	6	0.25-2	0.5	2

PHARMACOKINETICS/BIOAVAILABILITY

The proposed dose is a single 500-mg tablet taken once a day for 3 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 500 mg Ciprofloxacin (b) (4) once daily is 7.97 mg.h/L. This is about equal to the AUC for immediate-release ciprofloxacin 250 mg given twice daily. The peak plasma concentration (C_{max}) of Ciprofloxacin (b) (4) 500 mg given every 24 hours was 35% to 37% higher (Day 1 and Day 5, respectively) than the C_{max} following 250 mg immediate-release ciprofloxacin given every 12 hours. Median time to maximum plasma concentration (t_{max}) for Ciprofloxacin (b) (4) was 1.5 hours under fasting conditions, which was comparable to that of immediate-release ciprofloxacin. The elimination half-lives of both formulations were approximately 5 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 (b) (4) 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)

* median (range)

No clinically relevant food effect was seen when Ciprofloxacin (b) (4) was given after a high-fat meal, a low-fat meal, or under fasted conditions.

The amount of ciprofloxacin excreted unchanged in urine was virtually the same after administration of Ciprofloxacin (b) (4) and the corresponding immediate-release ciprofloxacin treatment given twice daily. However, significantly higher urinary ciprofloxacin concentrations were reached for Ciprofloxacin (b) (4) in the period up to 12 hours post dose as compared to the corresponding immediate-release formulation. In the post-treatment sample collected 24 to 28 hours after the last dose of Ciprofloxacin (b) (4), the mean urinary concentration was 11 μg/mL (range 3.3 μg/mL to 33.2 μg/mL). This lowest value (3.3 μg/mL) is over 100 times the MIC_{90} for *Escherichia coli*, the most common urinary tract pathogen. TABLE 5 shows the urinary concentrations over time for the two formulations.

TABLE 5
Mean (± SD) Urinary Concentrations (μg/mL) of Ciprofloxacin

	0-4 hours	4-8 hours	8-12 hours	12-24 hours	24-28 hours
Day 1 Cipro (b) (4)	338 ± 244	137 ± 75	57 ± 48	27 ± 14	
Day 1 Cipro IR*	161 ± 79	65 ± 38	27 ± 17	123 ± 50	
Day 5 Cipro (b) (4)	368 ± 267	166 ± 90	53 ± 40	30 ± 19	11 ± 8
Day 5 Cipro IR	196 ± 94	82 ± 51	31 ± 22	128 ± 50	29 ± 12

* IR = Immediate-release ciprofloxacin; collection times for this formulation (given BID) are referenced to the first dose of a 24-hour cycle.

RESULTS FROM CLINICAL TRIAL

STUDY 100346

This study was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter trial, conducted in the United States in adult female patients (ages 18 to 65 years) with uncomplicated urinary tract infections (UTI).

A total of 452 patients were randomized to the Ciprofloxacin (b) (4) (500 mg orally, once a day for 3 days) treatment group. Of these, 444 (98%) patients received at least one dose of Ciprofloxacin (b) (4) and were evaluable for safety. The remaining 8 patients did not receive any study drug and, therefore, were excluded from the safety analysis. A total of 453 patients were randomized to the control treatment group (Cipro® 250 mg orally, twice a day for 3 days). Of these 453 patients, 6 did not receive study drug.

Of the 905 patients who were randomized to the study, 881 completed the study and 24 (3%) discontinued. In this study urine specimens for culture were processed for susceptibility testing. Infecting organisms had a pre-therapy colony count of $\geq 10^5$ CFU/mL. These pathogens were identified and minimum inhibitory concentrations (MICs) for the study drug were determined. Identification and MICs were also determined for infecting organisms that were isolated from cultures performed during or after treatment if the colony count was $\geq 10^4$ CFU/mL. There were 199 patients in the Ciprofloxacin (b) (4)

500-mg treatment group and 223 patients in the Cipro® 250-mg treatment group who were in the microbiologically valid for efficacy population. TABLE 6 summarizes the microbiological outcome for these patients at the test-of-cure visit.

TABLE 6
Microbiological Outcome at the Test-of-Cure Visit
(Valid for Efficacy Population)

	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days N = 199	Cipro® 250 mg PO BID x 3 days N = 223
Eradication (%)	188 (94.5%)	209 (93.7%)
Persistence (%)	8 (4.0%)	11 (4.9%)
New Infection (%)	3 (1.5%)	3 (1.3%)

These data indicate that ciprofloxacin (b) (4) 500-mg once daily for 3 days eradicates uropathogens at about the same rate as ciprofloxacin 250-mg tablets twice a day for 3 days.

Results for the microbiological outcome at the late follow-up visit are summarized in TABLE 7. Continued eradication rates between the two treatment groups were similar. Nine patients in the Ciprofloxacin (b) (4) group and 3 patients in the control group had an indeterminate microbiological outcome at the late follow-up visit, because they received a systemic antibacterial agent with presumptive coverage against uropathogens between the test-of-cure and the late follow-up visit.

TABLE 7
Microbiological Outcome at the Late Follow-Up Visit
(Valid for Efficacy Population)

	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days N = 199	Cipro® 250 mg PO BID x 3 days N = 223
Continued Eradication (%)	151 (75.9%)	165 (74.0%)
Eradication with Recurrence (%)	14 (7.0%)	17 (7.6%)
Persistence (%)	8 (4.0%)	11 (4.9%)
New Infection (%)	3 (1.5%)	10 (4.5%)
Indeterminate (%)	23 (11.6%)	20 (9.0%)

In the valid for efficacy population, the microbiological and clinical cure rates were 94.5% and 95.5% for the Ciprofloxacin (b) (4) group, and 93.7% and 92.7% for the control group, respectively. For 92% of the patients in both groups, the clinical and microbiological outcome assessments were either both successful or both unsuccessful. There were 15 patients with microbiological eradication and clinical failure, 10 patients with microbiological persistence and clinical cure, and 5 patients with new infections and clinical cures (out of six total patients with new infections). There were slightly more discordant observations in the control group than in the Ciprofloxacin (b) (4) group. Of the patients in the Ciprofloxacin (b) (4) group who had eradication of their original causative uropathogens, 97% (182/188) also had a clinical cure. TABLE 8 compares the clinical and microbiological outcomes.

TABLE 8
Clinical Outcome by Microbiological Outcome at the Test-of-Cure Visit
(Valid for Efficacy Population)

Microbiological Outcome	Clinical Outcome	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days	Cipro® 250 mg PO BID x 3 days
Eradication	Cure (%)	182 (96.8%)	196 (93.8%)
	Failure (%)	5 (2.7%)	10 (4.8%)
	Indeterminate (%)	1 (0.5%)	3 (1.4%)
Persistence	Cure (%)	5 (62.5%)	5 (45.5%)
	Failure (%)	3 (37.5%)	6 (54.5%)
New Infection	Cure (%)	2 (66.7%)	3 (100.0%)
	Failure (%)	1 (33.3%)	0

TABLE 9 shows the microbiological outcome in the intent-to-treat population of patients who had positive pre-therapy cultures. As was the case in the efficacy population, the eradication rates between the Ciprofloxacin (b) (4) treatment group and the control treatment group are about equal.

TABLE 9
Microbiological Outcome at the Test-of-Cure Visit and the Late Follow-Up Visit
(Intent-to-Treat Population with Positive Pre-Therapy Urine Cultures)

	Ciprofloxacin (b) (4) 500 mg PO QD x 3 days N = 199	Cipro® 250 mg PO BID x 3 days N = 223
Test-of-Cure Visit		
Eradication (%)	193 (86.5%)	215 (87.4%)
Persistence (%)	9 (4.0%)	12 (4.9%)
New Infection (%)	4 (1.8%)	3 (1.2%)
Indeterminate (%)	17 (7.6%)	16 (6.5%)
Late Follow-Up Visit		
Continued Eradication (%)	159 (71.3%)	175 (71.1%)
Eradication with Recurrence (%)	16 (7.2%)	17 (6.9%)
Persistence (%)	9 (4.0%)	12 (4.9%)
New Infection (%)	6 (2.7%)	10 (4.1%)
Indeterminate (%)	33 (14.8%)	32 (13.0%)

TABLE 10 shows the microbiological and clinical results in the Ciprofloxacin (b) (4) arm of the study by pathogen. TABLE 11 shows the same information for the control treatment group.

TABLE 10
Microbiological and Clinical Responses at Test-of-Cure in Ciprofloxacin (b) (4) Arm

Organism	Microbiological Response		Clinical Response	
	Eradication (%)	Persistence (%)	Cure (%)	Failure (%)
Escherichia coli	156 (97.5%)	4 (2.5%)	153 (96.2%)	6 (3.8%)
Klebsiella pneumoniae	7 (77.8%)	2 (22.2%)	7 (77.8%)	2 (22.2%)
Proteus mirabilis	11 (91.7%)	1 (8.3%)	11 (91.7%)	1 (8.3%)
Proteus vulgaris	1	0	1	0
Enterobacter cloacae	2	0	2	0
Enterobacter aerogenes	2	0	2	0
Stenotrophomonas maltophilia	1	0	1	0
Enterococcus faecalis	10 (90.9%)	1 (9.1%)	10 (90.9%)	1 (9.1%)
Staphylococcus saprophyticus	5 (83.3%)	1 (16.7%)	6 (100%)	0
TOTAL	**195 (95.6%)**	**9 (4.4%)**	**193 (95.1%)**	**10 (4.9%)**

TABLE 11
Microbiological and Clinical Responses at Test-of-Cure in Ciprofloxacin 250-mg BID Arm

Organism	Microbiological Response		Clinical Response	
	Eradication (%)	Persistence (%)	Cure (%)	Failure (%)
Escherichia coli	176 (97.2%)	5 (2.8%)	166 (93.3%)	12 (6.7%)
Klebsiella pneumoniae	11 (78.6%)	3 (21.4%)	10 (71.4%)	4 (28.6%)
Klebsiella ornithinolytica	2	2	2	2
Proteus mirabilis	7 (100%)	0	7 (100%)	0
Enterobacter cloacae	2	0	2	0
Enterobacter aerogenes	3	0	3	0
Citrobacter koseri	2	0	2	0
Enterococcus faecalis	17 (81.0%)	4 (19.0%)	21 (100%)	0
Staphylococcus saprophyticus	7 (100%)	0	7 (100%)	0
TOTAL	**227 (94.2%)**	**14 (5.8%)**	**220 (92.4%)**	**18 (7.6%)**

TABLE 12 shows the eradication rate by MIC for each of the uropathogens. All MICs were ≤2 μg/mL, except for one *Escherichia coli* isolate with a MIC of 16 μg/mL. This isolate was not eradicated. The eradication rate did not seem to be related to the MIC value except for this one isolate at 16 μg/mL.

TABLE 11
Microbiological Responses by MIC

Organism	MIC (μg/mL)	Outcome	Ciprofloxacin (b) (4) 500 mg QD		Ciprofloxacin 250 mg BID	
			Number	%	Number	%
Staphylococcus saprophyticus	0.25	Eradication	3	100	5	100
	0.5	Eradication	2	100	2	100
	2	Persistence	1	100	0	0
	ALL	Eradication	5	83.3	7	100
		Persistence	1	16.7	0	0
Enterococcus faecalis	0.5	Eradication	4	100	7	87.5
		Persistence	0	0	1	12.5
	1	Eradication	5	83.3	10	83.3
		Persistence	1	16.7	2	16.7
	2	Eradication	1	100	0	0
		Persistence	0	0	1	100
	ALL	Eradication	10	90.9	17	81.0
		Persistence	1	9.1	4	19.0
Escherichia coli	0.008	Eradication	14	100	11	100
	0.015	Eradication	95	97.9	102	97.1
		Persistence	2	2.1	3	2.9
	0.03	Eradication	34	100	51	100
	0.06	Eradication	3	100	4	80.0
		Persistence	0	0	1	20.0
	0.12	Eradication	7	100	4	100
	0.25	Eradication	1	100	2	66.7
		Persistence	0	0	1	33.3
	0.5	Eradication	1	50.0	1	100
		Persistence	1	50.0	0	0
	1	Eradication	1	100	0	0
	2	Eradication	0	0	1	100
	16	Persistence	1	100	0	0
	ALL	Eradication	156	97.5	176	97.2
		Persistence	4	2.5	5	2.8
Klebsiella pneumoniae	0.015	Eradication	1	100	0	0
	0.03	Eradication	3	75.0	7	87.5
		Persistence	1	25.0	1	12.5
	0.06	Eradication	3	75.0	4	66.7
		Persistence	1	25.0	2	33.3
	ALL	Eradication	7	77.8	11	78.6
		Persistence	2	22.2	3	21.4
Klebsiella ornithinolytica	0.015	Eradication	0	0	1	100
	0.03	Eradication	0	0	1	100
	ALL	Eradication	0	0	2	100

TABLE 11 (Continued)
Microbiological Responses by MIC

Organism	MIC (μg/mL)	Outcome	Ciprofloxacin (b) (4) 500 mg QD		Ciprofloxacin 250 mg BID	
			Number	%	Number	%
Proteus mirabilis	0.015	Eradication	3	100	2	100
	0.03	Eradication	8	88.9	5	100
		Persistence	1	11.1	0	0
	ALL	Eradication	11	91.7	7	100
		Persistence	1	8.3	0	0
Proteus vulgaris	0.03	Eradication	1	100	0	0
	ALL	Eradication	1	100	0	0
Enterobacter cloacae	0.008	Eradication	1	100	0	0
	0.015	Eradication	1	100	1	100
	0.06	Eradication	0	0	1	100
	ALL	Eradication	2	100	2	100
Enterobacter aerogenes	0.015	Eradication	0	0	3	100
	0.03	Eradication	1	100	0	0
	0.06	Eradication	1	100	0	0
	ALL	Eradication	2	100	3	100
Citrobacter koseri	0.008	Eradication	0	0	1	100
	0.015	Eradication	0	0	1	100
	ALL	Eradication	0	0	2	100
Stenotrophomonas maltophilia	0.015	Eradication	1	100	0	0
	ALL	Eradication	1	100	0	0

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 uncomplicated UTI infections. The applicant has also listed *Staphylococcus aureus and Staphylococcus epidermidis*. These two Gram-positive organisms are usually not associated with uncomplicated 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 14-17.

REFERENCE

1. Sahm DF, Thornsberry C, Kelly LJ, Jones ME, Karlowsky JA. *In vitro* activities of commonly used antibiotics against prevalent uropathogens: Implications for empiric therapy. Infections in Urology 2001;**14(3):**59-67.

RECOMMENDATIONS

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 uncomplicated UTI infections.

2. (b) (4) should be revised to *Citrobacter koseri.*

3. In the Susceptibility Tests subsection the two sentences that read (b) (4) should be revised to read "For testing Enterobacteriaceae, *Staphylococcus* species, and *Enterococcus* species."

4. 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 levofloxacin."

The Microbiology subsection should, therefore, read as follows:
Proposed additions are double-underlined. Proposed deletions are indicated by a strikeout.

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 1 x 10^{-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 USUAGE** section.

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

Aerobic gram-negative microorganisms
Escherichia coli
(b) (4)
Proteus mirabilis

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 (b) (4) Tablets in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

(b) (4)

Aerobic gram-negative microorganisms

Citrobacter (b) (4) *koseri*	*Morganella morganii*
Citrobacter freundii	*Proteus vulgaris*
Edwardsiella tarda	*Providencia rettgeri*
Enterobacter aerogenes	*Providencia stuartii*
Enterobacter cloacae	*Serratia marcescens*
Klebsiella oxytoca	

Susceptibility Tests
Dilution techniques: Quantitative methods are used to determine antimicrobial minimum 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 powder. The MIC values should be interpreted according to the following criteria:

For testing (b) (4) -Enterobacteriaceae, *Enterococcus* species, 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 concentration 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 concentration 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

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 (b) (4) -Enterobacteriaceae, *Enterococcus* species, and *Staphylococcus species*:

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

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 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 quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	30-40
Staphylococcus aureus	ATCC 25923	22-30

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA # 21-473
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ENavarro
HFD-520/Pharm/SHundley
HFD-590/Chem/DMatecka
HFD-590/CSO/JSaliba

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/s/

Peter Dionne
5/31/02 02:09:46 PM
MICROBIOLOGIST

Shukal signed 5/29/02; Ken signed 5/29/02

Shukal Bala
6/2/02 04:06:35 PM
MICROBIOLOGIST

Kenneth Hastings
6/4/02 03:33:35 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA: 21-473
Review Number: 1
Date of Submission: 4/5/02
Information to Sponsor: Yes ( ) No (X)

Sponsor: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

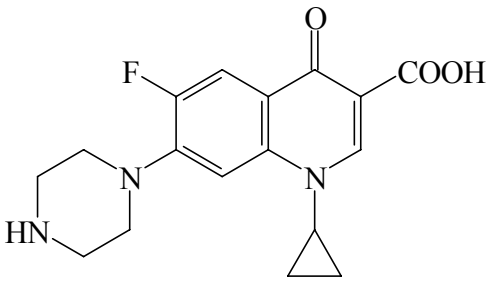
Manufacturer of Drug Substance:
Bayer AG
D-51368 Leverkusen
Germany

Reviewer: Stephen G. Hundley, Ph.D, DABT
Pharmacology/Toxicology Reviewer

Division: Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 9/16/02

Drug Product: Cipro XR
Generic Name: (b) (4)
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: (b) (4) (385.8 for the monochloride monohydrate salt)
Molecular Structure:



Relevant IND: 61,331

Drug Class: Antimicrobial Fluoroquinolone

Indication: Uncomplicated Urinary Tract Infection

Clinical Formulation: Extended Release Tablet

Route of Administration: Oral

Proposed Use: Single 500 mg Cipro XR tablet daily for three 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 uncomplicated urinary tract infection with Cipro XR at a 500 mg daily dose of ciprofloxacin for a period of three 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
9/27/02 09:51:10 AM
PHARMACOLOGIST

Kenneth Hastings
10/1/02 02:53:36 PM
PHARMACOLOGIST

Renata Albrecht
10/2/02 03:40:26 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

CHEMISTRY REVIEW(S)

NDA 21-473

Cipro XR (ciprofloxacin extended-release tablets)

BAYER CORPORATION
PHARMACEUTICAL DIVISION

Dorota Matecka
Division of Special Pathogen and Immunologic Drug Products, HFD-590

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-473

2. REVIEW #: 1

3. REVIEW DATE: 9-Dec-2002

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	4-Mar-2002
Amendment (NC)	18-Jul-2002
Amendment (BC)	7-Aug-2002
Amendment (BC)	20-Sep-2002
IR letter (email)	5-Nov-2002
Amendment (BC)	21-Nov-2002
Amendment (BC)	6-Dec-2002

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Original	4-Mar-2002
Amendment (NC)	18-Jul-2002
Amendment (BC)	7-Aug-2002
Amendment (BC)	20-Sep-2002
Amendment (BC)	21-Nov-2002
Amendment (BC)	6-Dec-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Bayer Corporation Pharmaceutical Division
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: 500 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

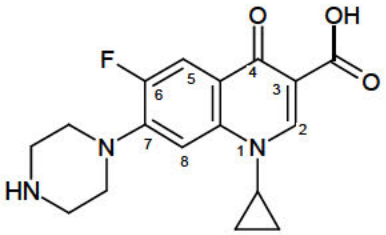
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

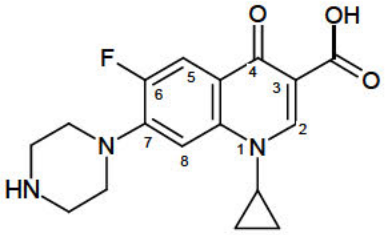
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ciprofloxacin [redacted] (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid); 331.4 (anhydrous basis); [redacted] (3.5 hydrate); $C_{17}H_{18}N_3FO_3$ (anhydrous basis); $C_{17}H_{18}N_3FO_3$ x 3.5 H_2O (3.5 hydrate)



Ciprofloxacin hydrochloride (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride monohydrate); 385.8; $C_{17}H_{18}N_3FO_3$ x HCl x H_2O



• HCl
• H_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-Nov-2002	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)	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

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	3-Dec-2002	Janine D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	Acceptable	10-Oct-2002	Dan Boring
Methods Validation	Not submitted yet	N/A	N/A
DMETS	Acceptable	31-Aug-2002	Carol Holquist
EA	Categorical exclusion	N/A	N/A
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-473

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 and CIPRO I.V.).

CIPRO XR tablets contains 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 24 months.

For the majority of chemistry, manufacturing and controls information regarding Ciprofloxacin (b) (4) hydrated form of ciprofloxacin base) 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 is (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 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)

B. Description of How the Drug Product is Intended to be Used

CIPRO XR tablets are available as 500-mg coated tablets for a once-a-day treatment of uncomplicated urinary tract infections. The tablets are packaged in three packaging configurations, HDPE 150 cc bottles (of 100 tablets), HDPE 120 cc bottles (of 50 tablets), and PVC/PVDC clear blisters.

The proposed expiration dating of 24 months as proposed by the applicant for CIPRO XR tablets 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). 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 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 and by the Division HFD-590. 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.

Several changes in the DESCRIPTION section of the labeling were recommended to the applicant.

III. Administrative

A. Reviewer's Signature

DFS (electronic)

B. Endorsement Block

Chemist: Dorota Matecka/11/25/02
Chemistry TL: Norman Schmuff
PM: Jouhayna Saliba

C. CC Block

35 page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

09-DEC-2002 FDA CDER EES Page 1 of 2

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21473/000
Org Code : 590
Priority : S

Sponsor: BAYER
400 MORGAN LANE
WEST HAVEN, CT 065164175

Stamp Date : 05-MAR-2002
PDUFA Date : 05-JAN-2003
Action Goal :
District Goal: 06-NOV-2002

Brand Name : CIPRO
(b) CIPROFLOXACIN/CIPROFLOXACIN HC
Estab. Name:
Generic Name: CIPROFLOXACIN/CIPROFLOXACIN HCL
Dosage Form: (CONTROLLED RELEASE TABLET)
Strength : 500 MG

FDA Contacts:			
J. SALIBA	Project Manager (HFD-590)	301-827-2387
D. MATECKA	Review Chemist (HFD-590)	301-827-2398
N. SCHMUFF	Team Leader (HFD-590)	301-827-2425

Overall Recommendation: ACCEPTABLE on 03-DEC-2002by J. D AMBROGIO(HFD-324) 301-827-0062

Establishment : CFN : 9610135 FEI : 3002806462
BAYER AG
LEVERKUSEN, , GM
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-NOV-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
Profile : TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-APR-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610496 FEI : 3002806447
BAYER AG
GESCHAFTSBEREICH PHARMA
WUPPERTAL-ELBERFELD, , GM D-42096
DMF No: 10353 8134 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

09-DEC-2002 FDA CDER EES Page 2 of 2

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-APR-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1216486 FEI : 1216486
BAYER CORP
400 MORGAN LANE
WEST HAVEN, CT 065164175
DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-APR-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9614785 FEI : 3002806461
BAYER SPA
120024
GARBAGNATE, MILAN, IT 1-20024
DMF No: 10353 AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-DEC-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

/s/

Dorota Matecka
12/10/02 10:21:26 AM
CHEMIST

Norman Schmuff
12/10/02 02:24:31 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

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:	21-473
Names of drug:	Cipro XR
Applicant:	Bayer
Indication:	Uncomplicated Urinary Tract Infection
Documents reviewed:	\\CDSESUB1\N21473\N_000\2002-03-04\
Project manager:	Jouhayna Saliba
	Susan Peacock
Clinical reviewer:	Regina Alivisatos, M.D.
Dates:	Received 03/04/02; user fee (10 months) 01/04/03
Statistical reviewer:	Ruthanna Davi, M.S.
Statistics team leader:	Karen Higgins, Sc.D.
Biometrics division director:	Mohammed Huque, Ph.D.

Keywords: NDA review, clinical studies, noninferiority

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 endpoints studied. This conclusion is robust against multiple sensitivity and subgroup analyses.

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 uncomplicated urinary tract infection. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily Modified Release 500 mg Tablets QD for 3 Days Versus Conventional Ciprofloxacin 250 mg Tablets BID for 3 Days in the Treatment of Patients with Uncomplicated Urinary Tract Infection". This study will be thoroughly reviewed within this document.

1.3 PRINCIPAL FINDINGS

The results of the controlled clinical trial submitted in support of the efficacy of Cipro XR indicate that Cipro XR is non-inferior to Cipro® in terms of the following endpoints.

- Bacteriologic response at the test-of-cure time point
- Bacteriologic response at the follow-up visit time point
- Clinical response at the test-of-cure time point
- Clinical response at the follow-up visit time point

These results remain consistent across both the per-protocol (PP) and modified intent-to-treat (mITT) analysis groups. In addition, these results are not dependent on the use of the amended test-of-cure (TOC) and follow-up time windows rather than those defined in the original protocol. Examination of the primary efficacy endpoint by age and race did not reveal any problematic subgroup differences. Also the 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 in the treatment of uncomplicated urinary tract infection. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily Modified Release 500 mg Tablets QD for 3 Days Versus Conventional Ciprofloxacin 250 mg Tablets BID for 3 Days in the Treatment of Patients with Uncomplicated Urinary Tract Infection". 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 women with confirmed uncomplicated urinary tract infections.

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 in the treatment of uncomplicated urinary tract infection. The following data sets were submitted electronically and were utilized in the review of this study. The reviewer found all data sets to be clearly documented and well organized.

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\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\clinev.xpt
\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\endpoint.xpt
\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\orgeff.xpt
\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\patinfo.xpt
\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\siteeff.xpt
\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\studymed.xpt
\\CDSESUB1\N21473\N_000\2002-03-04\crt\datasets\100346\visit.xpt

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 REVIEW OF STUDY NUMBER BAY-Q3939-100346

2.3.1.1 Study Design, Protocol, and Protocol Amendments

This was a multicenter, prospective, randomized, double-blind, parallel group, 3-day phase III clinical trial conducted at 58 centers in the United States. The primary objective of this study was to determine if Cipro XR 500 mg PO QD for three days was non-inferior to conventional ciprofloxacin (Cipro®) 250 mg PO BID for three days in the treatment of women with uncomplicated urinary tract infection (UTI).

Patients who fulfilled the following protocol-specified criteria were eligible for inclusion in the study.

- Non-pregnant women, 18 to 65 years of age;
- At least two of the following clinical signs and symptoms of an uncomplicated UTI: dysuria, frequency, urgency, and suprapubic pain
- Onset of symptoms ≤72 hours prior to study entry;
- One positive pretreatment clean-catch midstream urine culture at enrollment in the study, defined as $\geq 10^5$ CFU/mL (study treatment was permitted prior to the availability of urine culture results);
- Pyuria (defined as ≥10 leukocytes/mm^3 in unspun urine examined in a counting chamber) prior to study entry;
- Older women of childbearing potential, including women less than 1 year postmenopausal and/or not surgically sterilized, were required to use two reliable methods of contraception during exposure to study drug; and

- Culture and in vitro susceptibility testing was required on pretreatment clean-catch midstream urine specimens.

Patients who were male, were pregnant, nursing or not using medically accepted effective methods of birth control, or had a complicated UTI were excluded from the study. The exclusion criteria were not limited to these three items. (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 randomly assigned (in a 1:1 ratio without blocks) to receive one of the following two treatments.

Cipro XR 500 mg PO QD for three days or
Cipro® 250 mg PO BID for three days

The primary efficacy variable was defined to be the bacteriological response at the test-of-cure visit. 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. All categories except eradication were considered failures in the analysis.

Eradication: A urine culture taken within the posttherapy window of Days +4 to +11 showed that all uropathogens isolated at study entry in a quantity >=10 5 CFU/mL were reduced to <10 4 CFU/mL.
Persistence: A urine culture taken any time after the completion of therapy grew >=10 4 CFU/mL of the original uropathogen.
Superinfection: a urine culture grew > =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 isolated at baseline at a level >=10 5 CFU/mL, was present at a level >=10 5 CFU/mL anytime after treatment was completed.
Indeterminate: Patients in whom a bacteriological assessment was not possible to determine. Reasons for indeterminate evaluation must have been documented.

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. All categories except continued eradication were considered failures in the analysis.

Continued Eradication: Causative organism(s) in quantities <10 4 CFU/mL at the test-of-cure and at late follow-up visits.
Persistence: Patients with a causative organism =10 4 CFU/mL noted at the test-of-cure visit (+4 to +11 days post-treatment) regardless of the results of the culture at the follow-up visit were to be carried forward.
Superinfection: A urine culture grew =10 5 CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active therapy, with symptoms of infection as previously stated.
Recurrence: Causative organism(s) in numbers <10 4 CFU/mL at the test-of-cure visit, but reappearance of the same organism(s) =10 4 CFU/mL before or at the late follow-up visit.
New Infection: A pathogen =10 5 CFU/mL other than the original microorganism found at baseline was present at a level =10 5 CFU/mL anytime after treatment was finished.
Indeterminate: Bacteriological outcome to study drug could not be evaluated for any reason (eg, post-treatment culture not obtainable). The reason must have been recorded in the CRF.

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. All categories of the clinical outcome at the TOC visit were considered failures except clinical cure.

Clinical Cure: Disappearance or improvement of acute signs and symptoms of infection such that alternative antimicrobial therapy was not required or administered.
Clinical Failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before the test-of-cure visit, or use of additional antimicrobial therapy for the current infection.
Indeterminate: Patients in whom clinical assessment was not possible to determine. The reason for the indeterminate evaluation must have been documented. Patients graded as indeterminate at this visit were invalid for efficacy evaluation.

Clinical outcome at the follow-up visit was graded as continued clinical cure, failure, relapse, indeterminate. As with the other efficacy endpoints, all categories of the clinical outcome at the follow-up time point were considered failures except continued clinical cure.

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: Patients carried forward from the test-of-cure visit.
Relapse: Reappearance of signs and symptoms of an uncomplicated UTI considered to be related to an infectious (bacterial) process such that institution of alternative antimicrobial therapy was required.
Indeterminate: Patients in whom clinical assessment was not possible to determine. The reason for indeterminate evaluation must have been documented.

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 December 20, 2001 (approximately 1 month after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 4 to 11 days post-treatment and the follow-up visit window to 25 to 50 days post-treatment. Under the newly amended time frames, 26 subjects who previously were ineligible for the efficacy analysis at the test-of-cure visit were now considered eligible for analysis. In addition, there were 30 subjects with follow-up visits that fell outside the protocol-specified time frame but within the amended window. 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 because a large number of patients had test-of-cure evaluations performed outside the protocol-specified 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 test-of-cure visit in women with uncomplicated UTI. A two-sided 95% confidence interval for the weighted difference between treatment groups was to be constructed, using Mantel-Haenszel weights (weighting by center). 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 center 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 population defined as subjects meeting all of the following criteria.

- All inclusion/exclusion criteria were met;

- Study drug was given for a minimum of two days (four doses) if the clinical outcome at the test-of-cure visit was failure, or a minimum of three days (at least five doses or eight tablets) if the clinical outcome at the test-of-cure visit was Cure;
- All bacteriological outcomes were determined at the test-of-cure visit unless the patient was an early treatment failure (patients with a response of Indeterminate at the test-of-cure 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 test-of-cure visit unless the patient was a treatment failure;
- 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 was also planned including all patients who received at least one dose of study drug and had a baseline pathogen. Patients with missing or indeterminate efficacy evaluations were to be included and counted as nonsuccesses in all efficacy analyses carried out in the mITT population. While the valid-for-efficacy results were designated by 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 valid-for-efficacy group. Therefore this review will include discussion of the results from both analysis groups.

The protocol originally specified that 584 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 90%,
- The smallest clinically meaningful difference between treatments (delta) is 10%, and
- The subject validity rate is 80%.

During the study, it became clear that the validity rate would be much lower than 80% because the rate of pretreatment urine culture results with $\geq 10^5$ CFU/mL of a causative organism was lower than originally anticipated. The protocol was amended twice to address this. First, approximately five months after the finalization of the protocol the sample size was revised using an assumed validity rate of 60% which resulted in the need for 778 patients to be enrolled in order to obtain 466 valid patients. Approximately 3½ months later, the assumed validity rate was again revised, this time to 50%. In addition, an alternate method for sample size calculation was used (Farrington et. al[2]). This resulted in the need for 820 patients to be enrolled in order to obtain the now necessary 410 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.

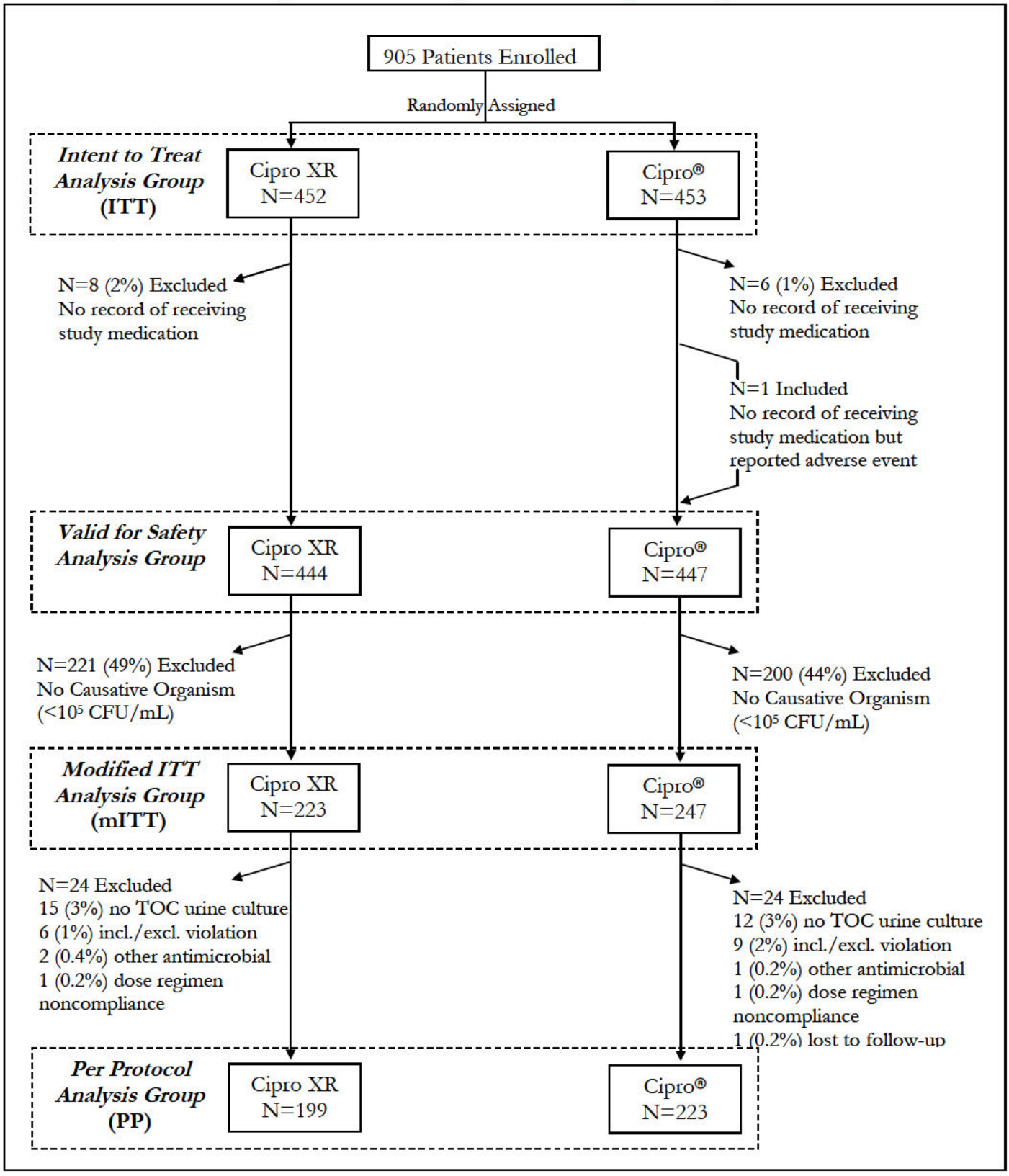
[1] Rodary C, Com-Nougue C, Tournade MF. How to establish equivalence between treatments: a one-sided clinical trial in pediatric oncology. *Stat Me*d. 1989;8:593-8.
[2] Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Me*d. 1990;9:1447-54.

In the course of field inspections, FDA investigators reported that ineligible subjects might be being used in the primary and secondary efficacy analyses, as records indicated that certain subjects did not meet the pretreatment urine culture requirement of having $\geq 10^5$ CFU/mL of a causative organism. Assessment of the electronic data by this reviewer did not substantiate this observation. According to the electronic data submitted with the NDA, the pretreatment urine culture requirement had been met for all subjects included in the efficacy analyses. The reader should note however, that discrepancies between the electronic data set and actual data observed could exist and would not have been identified by this analysis. Please refer to the clinical review of this application for more discussion of this item.

2.3.1.2 Results

This study enrolled 905 patients at 58 centers. Four hundred fifty two were randomly assigned to treatment with Cipro XR and 453 were randomly assigned to treatment with Cipro®. Patient inclusion in or exclusion from the *intent-to-treat* (ITT), *valid for safety*, *modified intent-to-treat* (mITT), and *per-protocol* (PP) analysis data sets are described in Figure 1.

Figure 1: Patient Disposition and Analysis Groups



As indicated in Figure 1, fourteen subjects were excluded from the valid for safety analysis group, as there was no record of them receiving study medication. One additional patient, for whom records did not indicate that study medication had been received, reported an adverse event. This subject was included in the valid for safety group. The only reason for further exclusions from the mITT analysis group in both treatments groups was no causative organism reported in a quantity $\geq 10^5$. The Cipro XR group had a slightly higher rate of patients (49%) with no causative organisms at a level $\geq 10^5$ CFU/mL compared with the Cipro® group (44%). Further exclusions from the PP analysis group were made for the follow reasons; no TOC urine culture, violation of inclusion and/or exclusion criteria, use of another antimicrobial, noncompliance with the dosage regimen, and lost to follow-up. The frequencies of these exclusions were similar between the two treatment groups.

Demographic and baseline variables (including causative orgainsm) for the PP and valid for safety analysis groups are summarized in Table 1.

Table 1: Demographic and Baseline Variables Summary Statistics

		PP Analysis Group		Safety Analysis Group	
		Cipro XR N=199	Cipro® N=223	Cipro XR N=444	Cipro® N=447
Age (years)	**Mean (Median)**	34.3 (33.0)	35.1 (34.0)	35.2 (33.0)	34.8 (33.0)
	Range	18.0 – 64.0	12.7 – 65.0	18.0 – 79.0	18.0 – 76.0
Weight (kg)	**Mean (Median)**	70.5 (65.9)	70.5 (67.3)	71.1 (65.9)	70.8 (67.5)
	Range	39.5 – 159.5	41.4 – 134.1	39.5 – 159.5	41.4 – 145.0
Race	**Caucasian**	154 (77%)	179 (80%)	350 (79%)	358 (80%)
	Black	17 (9%)	18 (8%)	43 (10%)	37 (8%)
	Asian	5 (3%)	5 (2%)	9 (2%)	12 (3%)
	American Indian	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
	Hispanic	21 (11%)	20 (9%)	39 (9%)	38 (9%)
	Other	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Duration of Infection	**1 day**	22 (11%)	37 (17%)	66 (15%)	69 (15%)
	2 days	92 (46%)	97 (43%)	189 (43%)	190 (43%)
	3 days	76 (38%)	79 (35%)	167 (38%)	171 (38%)
	4 days	9 (5%)	10 (4%)	22 (5%)	16 (4%)
	5 days	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Number of Episodes in Last 12 mo.	**None**	133 (67%)	155 (70%)	280 (63%)	284 (64%)
	One	51 (26%)	51 (23%)	122 (27%)	117 (26%)
	Two	15 (8%)	17 (8%)	41 (9%)	43 (10%)
	Three	0 (0%)	0 (0%)	1 (<1%)	3 (<1%)
Pre-therapy Causative Organisms (subj. may have >1 organism)	**Staphylococuss Saprophyticus**	6 (3%)	7 (3%)	8 (2%)	7 (2%)
	Enterococcus Faecalis	11 (6%)	21 (9%)	11 (2%)	21 (5%)
	Escherichia Coli	160 (80%)	181 (81%)	182 (41%)	201 (45%)
	Klebsiella Pheumoniae	9 (5%)	14 (6%)	10 (2%)	14 (3%)
	Klebsiella Ornithinolytica	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)
	Proteus Mirabilis	12 (6%)	7 (3%)	12 (3%)	10 (2%)
	Proteus Vulgaris	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
	Enterobacter Cloacae	2 (1%)	2 (<1%)	2 (<1%)	2 (<1%)
	Enterobacter Aerogenes	2 (1%)	3 (1%)	2 (<1%)	3 (1%)
	Citrobacter Koseri	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)
	Stenotrophomonas Maltophilia	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
	No baseline pathogen	NA	NA	221 (50%)	200 (45%)

There were no statistically significant differences between treatment groups in these variables in either the PP or valid for safety analysis groups. Since the mITT group includes subjects in the PP analysis group with only an additional 24 Cipro XR and 23 Cipro® subjects, the summary statistics for demographic and baseline characteristics using the mITT analysis group are very similar to that of the PP analysis group. Therefore these results are not included in this review.

Bacteriological response at the test-of-cure visit is the primary efficacy variable. Bacteriological response at the follow-up visit and clinical responses at the test-of-cure and follow-up visits are considered secondary variables. These results are summarized in Table 2 for both the PP and mITT analysis groups.

Table 2

	PP Analysis Group		mITT Analysis Group*	
	Cipro XR N=199	Cipro® N=223	Cipro XR N=223	Cipro® N=247
Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)				
Eradication	188 (94.5%)	209 (93.7%)	188 (84.3%)	209 (84.6%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-3.9%, 5.6%)		(-7.6%, 6.2%)	
Uncorrected	(-3.5%, 5.1%)		(-7.1%, 5.8%)	
Bacteriologic Success at the Follow-up Time Point (Secondary Efficacy Endpoint)				
Eradication	151 (75.9%)	165 (74.0%)	151 (67.7%)	165 (66.8%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-6.4%, 10.5%)		(-7.9%, 9.5%)	
Uncorrected	(-5.9%, 10.1%)		(-7.5%, 9.1%)	
Clinical Response at the Test-of-Cure Time Point (Secondary Efficacy Endpoint)				
Success	189 (95.0%)	206 (92.4%)	189 (84.8%)	206 (83.4%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-2.2%, 7.9%)		(-5.8%, 8.4%)	
Uncorrected	(-1.7%, 7.5%)		(-5.4%, 7.9%)	
Clinical Response at the Follow-up Time Point (Secondary Efficacy Endpoint)				
Success	166 (83.4%)	187 (83.9%)	166 (74.4%)	187 (75.7%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-6.8%, 7.5%)		(-9.2%, 7.1%)	
Uncorrected	(-6.4%, 7.0%)		(-8.8%, 6.6%)	

* Patients in the mITT analysis group with no urine culture (when applicable), violation of inclusion and/or exclusion criteria, use of another antimicrobial, noncompliance with the dosage regimen, or who were lost to follow-up were counted as nonsuccesses in this efficacy analysis.

Interpretation the results in Table 2 (utilizing a protocol-defined delta of 10%) indicate that Cipro XR is non-inferior to Cipro® in terms of all the endpoints examined, including the

TOC bacteriologic response (primary endpoint) as well as the follow-up bacteriological response and clinical responses at both visits (secondary endpoints).

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 December 20, 2001 (approximately 1 month after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 4 to 11 days post-treatment and the follow-up visit window to 25 to 50 days post-treatment. Under the newly amended time frames, 26 subjects who previously were ineligible for the efficacy analysis at the test-of-cure visit were now considered eligible for analysis. In addition, there were 30 subjects with follow-up visits that fell outside the protocol-specified time frame but within the amended window. 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 because a large number of patients had test-of-cure evaluations performed outside the protocol-specified window, possibly indicating that examination of the efficacy data had begun. This reviewer conducted the analyses of the bacteriologic 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 numerical results of the original protocol-defined analysis are summarized in Table 3.

Table 3**

	PP Analysis Group		mITT Analysis Group*	
	Cipro XR N=187	Cipro® N=209	Cipro XR N=211	Cipro® N=233
Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)				
Eradication	176 (94.1%)	195 (93.3%)	176 (82.9%)	195 (83.7%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-5.9%, 5.0%)		(-8.6%, 5.9%)	
Uncorrected	(-5.4%, 4.5%)		(-8.1%, 5.5%)	
Bacteriologic Success at the Follow-up Time Point (Secondary Efficacy Endpoint)				
Eradication	144 (77.0%)	153 (73.2%)	144 (68.2%)	153 (65.7%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-5.8%, 12.0%)		(-7.4%, 11.0%)	
Uncorrected	(-5.3%, 11.5%)		(-6.9%, 10.5%)	

* Patients in the mITT analysis group with no urine culture, violation of inclusion and/or exclusion criteria, use of another antimicrobial, noncompliance with the dosage regimen, or who were lost to follow-up were counted as nonsuccesses in this efficacy analysis.

** 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 4 displays the bacteriological response at the TOC time point by demographic variables. With only two exceptions (Cipro XR treated subjects ages 31 to 44 and Cipro XR treated Hispanic subjects), the eradication rates for each treatment group appear to be similar within subgroups. In the two subgroups mentioned where there are relatively large numerical differences between treatment groups in eradication rates, this reviewer is in agreement with the sponsor that these results are likely due to random variation.

Table 4: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Age and Race

	PP Analysis Group	
Eradication Rate	**Cipro XR**	**Cipro®**
All Patients	188/199 (94.5%)	209/223 (93.7%)
Age		
18 to 30 years	83/84 (98.8%)	92/97 (94.8%)
31 to 44 years	64/74 (86.5%)	69/71 (97.2%)
45 to 65 years	41/41 (100.0%)	48/55 (100.0%)
Race		
Caucasian	146/154 (94.8%)	166/179 (92.7%)
Black	17/17 (100.0%)	18/18 (100.0%)
Asian	5/5 (100.0%)	5/5 (100.0%)
American Indian	1/1 (100.0%)	1/1 (100.0%)
Hispanic	18/21 (85.7%)	19/20 (95.0%)
Uncodable	1/1 (100.0%)	0/0 (NA)

Table 5 displays the bacteriological response at the TOC time point by organism. The eradication rates were similar in the two treatment groups for each of the organisms.

Table 5: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Organism

	PP Analysis Group	
Eradication Rate	**Cipro XR**	**Cipro®**
Staphylococcus Saprophyticus	5/6 (83.3%)	7/7 (100.0%)
Enterococcus Faecalis	10/11 (90.9%)	17/21 (81.0%)
Escherichia Coli	156/160 (97.5%)	176/181 (97.2%)
Klebsiella Pneumoniae	7/9 (77.8%)	11/14 (78.6%)
Klebsiella Ornithinolytica	0/0 (NA)	2/2 (100.0%)
Proteus Mirabilis	11/12 (91.7%)	7/7 (100.0%)
Proteus Vulgaris	1/1 (100.0%)	0/0 (NA)
Enterobacter Cloacae	2/2 (100.0%)	2/2 (100.0%)
Enterobacter Aerogenes	2/2 (100.0%)	3/3 (100.0%)
Citrobacter Koseri	0/0 (NA)	2/2 (100.0%)
Stenotrophomonas Maltophilia	1/1 (100.0%)	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.

- Sample size revisions as a result of overestimating the validity rate (ref: *Section 2.3.1.1*)
- Redefinition of acceptable time windows for collection of TOC and follow-up efficacy data (ref: *Sections 2.3.1.1 and 2.3.1.2*)

2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The results of this study indicate that Cipro XR is non-inferior to Cipro® in terms of the following endpoints.

- Bacteriologic response at the test-of-cure time point
- Bacteriologic response at the follow-up visit time point
- Clinical response at the test-of-cure time point
- Clinical response at the follow-up visit time point

These results remain consistent across both the PP and mITT analysis groups. In addition, these results are not dependent on the use of the amended TOC and follow-up time windows rather than those defined in the original protocol. Examination of the primary efficacy endpoint by age and race did not reveal any problematic subgroup differences. Also the 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 endpoints studied. This conclusion is robust against multiple sensitivity and subgroup analyses.

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

/s/

Ruth Davi
12/10/02 06:00:28 PM
BIOMETRICS

Karen Higgins
12/12/02 11:04:27 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-473

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-473	Efficacy Supplement Type SE-	Supplement Number
Drug: **CIPRO® XR**	Applicant: **Bayer 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:	(X) Standard ( ) Priority
• Review priority	
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**January 3, 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	(X) Paid
• User Fee	
• 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)	( ) Yes (X) No
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	
• 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	(X) Verified
• Information: Verify that patent information was submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	
• 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)	(X) Yes ( ) 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)	**February 13, 2001 (CMC) & May 2, 2001**
• Pre-NDA meeting (indicate date)	**January 15, 2002 & February 15, 2002 (CMC)**
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	**June 6, 2002**

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)*	**January 7, 2003**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**June 4, 2002**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**January 7, 2003**
❖ 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)*	**December 2, 2002**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**December 16, 2002**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**X**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**December 10, 2002**
❖ Environmental Assessment – **See CMC review**	
• Categorical Exclusion *(indicate review date)*	**December 10, 2002**
• 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 3, 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)*	**October 2, 2002**
❖ 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

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
5/14/03 02:58:09 PM

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 (b) (4)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N #21-473

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
4265

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)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew L. Vesterman	Deputy Director, Regulatory Affairs	3/4/02

FORM FDA 3397 (3/01)

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

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Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

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(203) 812-5172

3. PRODUCT NAME

Cipro (b) (4)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N #21-473

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
4265

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

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(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, on reverse side before checking box.)

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☐ 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)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew S. Vesterman	Deputy Director, Regulatory Affairs	3/4/02

FORM FDA 3397 (3/01)

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 American Regulatory Affairs
Bayer Corporation

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 Taylor
Vice President, North American Regulatory Affairs
Bayer Corporation

Section 14 – Patent Certification

All investigators relied upon by Bayer 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.

EXCLUSIVITY SUMMARY for NDA # 21-473 SUPPL #

Trade Name CIPRO® XR Generic Name ciprofloxacin extended release tablets
Applicant Name Bayer Corporation HFD- 590
Approval Date December 13, 2002

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/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      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.

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 # 100346

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 # ___100346

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: _____

_____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

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

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
2/14/03 03:58:09 PM

Jouhayna Saliba
2/10/03 03:11:58 PM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-473
Trade Name: Cipro (b) (4)
Generic Name: Ciprofloxacin / Ciprofloxacin HCL
Strength: 500mg tablets

Applicant: Bayer Corporation

Date of Application: March 4, 2002
Date of Receipt: March 5, 2002
Date of Filing Meeting: April 17, 2002
Filing Date: May 4, 2002

Indication requested: Uncomplicated UTI

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#_4265___
Clinical data? YES ___X____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: **January 3, 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? Date **2/14/2001** NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) **1/15/2002** 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: Held virtually 4/17/02

BACKGROUND
Cipro was already approved and this NDA is for a modified release formulation

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Regina Alivisatos
Statistical:	Ruthanna Davi
Pharmacology/Toxicology:	Stephen Hundley
Chemist:	Dorota Matecka
Environmental Assessment (if needed):	
Biopharmaceutical:	Joette Meyer
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
2/13/03 10:56:32 AM

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MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 24, 2002

TO: Jouhayna Saliba, Project Manager, HFD-510

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety

SUBJECT: Label Comprehension Study for Cipro (b) (4)
NDA 21-473

The attached memorandum summarizes the most important points DSRCS wishes to make about the label comprehension study.

{See appended electronic signature page}

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 24, 2002

TO: Jouhayna Saliba, Project Manager, HFD-590

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support (DSRCS), HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support (DSRCS), HFD-410
Office of Drug Safety (ODS)

SUBJECT: DSRCS Label Comprehension Comments for Cipro (b) (4)
NDA 21-473

These comments will cover the portion of the label comprehension study that deals with the questions to physicians about how Cipro (b) (4) is to be used and how distinguishable Cipro (b) (4) is from Cipro. We are not commenting here on responses from the pharmacists or on physicians' responses about useful sources of information. We are sending these comments without a complete written review so you will have our thoughts before the meeting with the sponsor.

Open-ended question about the indication
The results show that when asked what the product is used for, 36% of physicians in the study correctly stated it is for uncomplicated UTI's. Sixty-one percent (61%) said UTI's without specifying uncomplicated.

Direct questions
When asked direct questions about using the product for specific conditions, the percentages of **incorrect** responses ranged from 8% to 10%. Incorrect responses were those that did **not** say the product should **not** be used. They did not necessarily say that the product **could** be used, but they did not say it should not. Incorrect responses included mentions of bacteria or organisms that could be treated, as well as other unspecified responses.

	Incorrect
complicated UTI's	18%
lower respiratory tract infections	10%

sinusitis	8%

Hypothetical cases

In a series of hypothetical cases, incorrect percentages for uses that are not indicated ranged from 2% to 17%. Incorrect responses said that Cipro (b) (4) **could** be used, or they were incorrect for unspecified reasons.

	Incorrect
intra-abdominal infection	5%
prostatitis	11%
pharyngitis/tonsilitis	2%
uncomplicated UTI	0%
pyelonephritis	17%
gonococcal urethritis	4%

Dosing and administration questions

When the physicians were asked about dosing and whether the product could be broken or chewed, the incorrect responses were as follows:

	Incorrect
Q. 17- dosage, frequency, and duration—uncomplicated UTI	11%
Q. 25- dosage, frequency, and duration—uncomplicated UTI	6%
Q. 32- dosage, frequency, and duration—uncomplicated UTI	3%
Q. 30—dosage, frequency, duration for conventional Cipro (not clear which responses were correct) ?	
Q. 23/24—which is a once a day product? (Cipro (b) (4) Cipro, both, neither?)	5%
Q. 28/29/31—which appropriate for uncomplicated UTI? (Cipro (b) (4) Cipro, both, neither?)	1%
Q. 26—can the medicine be crushed?	13%
Q. 34—take more than 1/day if you miss a day?	7%
Q. 36—what to tell patient who misses a day?	4%

Distinguishable ratings

On a scale of 1-10, with 1 being not at all distinguishable and 10 being extremely distinguishable, 86% of physicians said the packages of Cipro and Cipro (b) (4) were distinguishable from each other at a level of 8 or above. However, on the same scale, only 55% said the names were distinguishable with a rating of 8 or above. This suggests that the names may not be well differentiated by physicians.

Discussion

Although the correct results are relatively high for most questions, we have some methodological concerns that may have contributed to the high scores. Some of these concerns were raised in our comments on the original protocol; others are new. While some of our recommendations were followed, others were not.

We had recommended that the series of three direct questions about using the product for different conditions be presented in a different manner. We recommended scenario

(hypothetical) questions or a checklist containing a number of conditions instead of the direct questions. Furthermore, all three questions presented situations in which the product should not be used, potentially establishing a nay-saying bias by which the pattern of the questions influences the responses.

It is not good practice to alert participants to the purpose of a study. Doing so detracts from the realism of the situation, which, already, is far from perfect. If we wanted to study how physicians would use the new product in the course of their practice, it would have been better not to tell them that fact. In this study, the interviewer stated "The manufacturer of ciprofloxacin wants to make sure that they have made clear to physicians the differences between this new product and the conventional Cipro tablets." This statement alerts participants to look for differences they might not ordinarily notice.

The interviewer provided participants specifically with pages from the PDR for conventional Cipro. This made conventional Cipro and all of its labeling more salient to the participants. In an actual patient situation, we do not know if physicians would bother to check the conventional Cipro labeling. Participants also had a PDR for reference. They could have used that if they wanted to look up conventional Cipro. Using the PDR better simulates what they would do in their offices if they needed information on conventional Cipro. It would have been better not to give participants conventional Cipro labeling separate from the PDR.

We recommended that when the participants examined the package insert that they not be given 10 minutes to do so. We believed that may have been too long. Instead, we suggested having the participants signal when they had finished examining the insert. The sponsor, however, gave them all 10 minutes. It is possible this gave participants much more time to think about the product than they would in a normal practice situation.

Recommendations

The sponsor provided a report from (b) (4) which made some useful recommendations about how to improve the label communication in some of the areas in which there were higher percentages of incorrect responses. However, for some issues, (b) (4) had no specific suggestions.

His suggestions include the following, and appear to be appropriate:

- The initial topic sentence in the indications section should emphasize the product is for uncomplicated UTI's.
- Explicitly state that the product has not been shown to be effective in infections other than uncomplicated UTI's.
- The wording about not crushing, chewing, or breaking the product should be highlighted.
- Promotional material should emphasize the dosing regimen.
- Perhaps more conventional brand name testing should be conducted for further data on the sufficiency of differences in the brand names of Cipro (b) (4) and Cipro.

DSRCS has the following additional suggestions:

- Edit the PPI so it is in the format the agency now recommends. Change wording that is in all capitals to bolded upper and lower case. All capitals is hard to read.
- If appropriate, clarify in the PI what "uncomplicated UTI" means.

Conclusion

There is evidence that some messages about Cipro (b) (4) are not well understood by physicians and that the product name may not be very distinguishable from conventional Cipro. Problems with the methodology somewhat reduce our confidence in the validity of the results that show generally high levels of understanding. The sponsor's consultant has provided some useful recommendations to strengthen the weak messages, however, we cannot be sure that they will help unless further study is done. DSRCS has provided some additional suggestions.

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/s/

Karen Lechter
5/24/02 10:54:38 AM
UNKNOWN

Anne Trontell
5/28/02 06:59:25 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 06/05/01	**DUE DATE:** 07/31/01	**OPDRA CONSULT #:** 01-0125

TO:
Renata Albrect, MD
Acting Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH:
Jouhayna Saliba
Project Manager
HFD-590

PRODUCT NAMES:	**SPONSOR:**
(b) (4) (Ciprofloxacin Extended-release Tablets) **500 mg** **and** (b) (4) (Alternate name)	Bayer Corporation Pharmaceutical Division
NDA: 21-473 and IND: 61,331	

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), DMETS has commented on the proposed names (b) (4) and the Division of Risk Evaluation has evaluated and commented on the proposed "Package Insert Comprehension/Package and Brand Name Assessment Study" for each proposed proprietary name.

DMETS RECOMMENDATION:
The Division of Drug Risk Evaluation reviewed the proposed study protocols and determined the sponsor does not completely address their stated study objectives (see attachment A for complete review). The Division of Medication Errors and Technical Support does not recommend the use of the proprietary names (b) (4) (b) (4)

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 480-8173

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 26, 2001

NDA NUMBER: 21-473
IND NUMBER: 61,331

NAME OF DRUG: (b) (4) (Ciprofloxacin Extended-release Tablets) 500 mg
(b) (4) (Ciprofloxacin Extended-release Tablets) 500 mg

NDA/IND HOLDER: Bayer Corporation Pharmaceutical Division

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), for assessment of the sponsors protocols entitled (b) (4) Package Insert Comprehension/Package and Brand Name Assessment Study" and (b) (4) Package Insert Comprehension/Package and Brand Name Assessment Study". DMETS was recently informed by the Division that (b) (4) will not be submitted as an NDA. However, the review provided by the Division of Risk Evaluation were completed prior to this knowledge and therefore contain content relating to (b) (4) Additionally, DMETS has also reviewed the proposed proprietary names (b) (4)

PRODUCT INFORMATION
The sponsor states that (b) (4) is a (b) (4) formulation of the currently marketed Cipro. (b) (4) will be available as 500 mg tablets for once daily administration. Both are indicated for the treatment of uncomplicated urinary tract infections caused by *Escherichia coli,* (b) (4) *Proteus mirabilis, or Staphylococcus saprophyticus*. The usual dosage is 500 mg once daily for 3 days.

II. SAFETY EVALUATOR RISK ASSESSMENT

A. ESTABLISHED NAME/FORMULATION ISSUES

The sponsor describes Cipro (b) (4) as a (b) (4) According to the sponsor, the tablet is designed as a two-layer tablet in which the first layer contains 35% of the drug substance and releases the drug within a short period of time after administration. The second layer contains 65% of the drug and has slower release characteristics for the drug substance than the immediate release tablet.

Upon review of the DESCRIPTION section of the Cipro (b) (4) package insert labeling we noted that Cipro (b) (4) contains ciprofloxacin hydrochloride and ciprofloxacin betaine hydrate. The currently marketed Cipro contains ciprofloxacin hydrochloride alone. The addition of the second active ingredient raises several questions. First, is "ciprofloxacin betaine hydrate" another salt of the active moiety ciprofloxacin? Alternatively, can "ciprofloxacin betaine hydrate" be considered a water of hydration or polymorph of ciprofloxacin? The answers to these questions will inevitably affect the established name of the product and discussion would follow regarding whether or not this new formulation could use "Cipro" as part of the proprietary name if deemed a different product. Finally, the term (b) (4) is not an approved dosage form descriptor according to the United States Pharmacopeia (USP). DMETS recommends this issue be forwarded to the CDER Labeling and Nomenclature Committee (LNC) for review and comment.

B. PROPRIETARY NAMES

"Cipro" is an approved proprietary name for ciprofloxacin hydrochloride and has been marketed by Bayer under NDA 19-537 since April 18, 1996. Therefore, (b) (4) were the only portions of the proposed proprietary names that were evaluated. DMETS does not recommend the use of the modifiers (b) (4) for the following reasons:

1. The Agency has reconsidered their approach in approving alternate proprietary names. Pursuant to a December 1, 2000, CDER policy meeting with the Center Director, Janet Woodcock, M.D. and senior management, DMETS will no longer recommend approval of different proprietary names by the same applicant or manufacturer for products that are essentially identical unless there is a public health risk or stigma associated with the use of the drug product. The Agency is concerned that the proliferation of proprietary names may be misleading and may also lead to product confusion resulting in medication errors and/or patient harm for the following reasons:

   Safety Concerns:

   •*Overdose:* Practitioners may become confused and not understand that the two products (with two different trade names) are identical. This may increase the risk of a patient being prescribed the same drug product by different physicians, resulting in an overdose or inadvertent exposure.

   •*Confusion/Misleading*: Trivialization of the adverse events and risks associated with the use of different proprietary names for the same active moiety. Patients may be falsely assured that the medication does not carry significant risks because the FDA has allowed its use for a relatively benign condition.

•*Medication errors:* The creation of a new proprietary name for a new indication of an essentially identical drug product adds unnecessarily to the growing number of proprietary names in the United States. This proliferation of numerous proprietary names may increase the likelihood of occurrence of medication errors resulting in patient injury due to sound-alike and/or look-alike confusion between products.

Other Concerns:
•*Management of ADE:* The increasing complexity to manage (regulatory) reports of adverse drug events associated with one active ingredient with two or more proprietary names.

2. The currently approved Cipro tablets can be utilized to treat severe complicated urinary tract infections and mild to moderate urinary tract infections dependent on the dosage. According to the package insert labeling, Cipro (b) (4) is *only* indicated for use in the treatment of uncomplicated urinary tract infections. (b) (4) is broad, does not clearly convey "Uncomplicated Urinary Tract Infections", and is therefore misleading.

3. "UTI" is a common medical abbreviation for urinary tract infection and urinary trypsin. "QD" is a standard medical abbreviation for "every day". The Agency has always considered the use of coined abbreviations in conjunction with proprietary names objectionable since they can be misinterpreted. We refer you to ASHP Guidelines on Preventing Medication Errors in Hospitals (Am J Hosp Pharm., Vol. 50, Feb 1993) and The CDER Labeling and Nomenclature Committee, Structure, Function, and Process (Drug Information Journal, Vol. 31, Nov 1997).

4. "QD" is a dangerous abbreviation to use because it is often misinterpreted as "QID" or "4 times a day". DMETS also believes the proposed proprietary name poses a significant risk for potential confusion between the immediate release dosage form and the proposed extended release formulation. The immediate release formulation is utilized to treat severe complicated urinary tract infections and mild to moderate urinary tract infections dependent on the dosage. Prescriptions for Cipro (b) (4) x 3 days could easily be misinterpreted as simply ciprofloxacin daily and filled with the immediate release dosage form which is not approved for a 24 hour dosing interval or three day treatment regimen.

5. We discourage including the dosage regimen in the proprietary name. As the product evolves, newer dosing schedules may be approved, which might conflict with the a once a day modifier.

6. It is not clear if this proposed formulation could be considered a delayed or extended release formulation of the currently marketed Cipro or classified as a different chemical entity. If it is considered a delayed or extended release formulation of Cipro, then current nomenclature standards would include an extended-release modifier to the CIPRO name (CIPRO- (b) (4) tc.) rather than an indication of use or dosing interval.

C. PROTOCOLS

The Division of Drug Risk Evaluation in the Office of Drug Safety reviewed the proposed protocols for Cipro [redacted] (b) (4) The following represents the "Executive Summary" comments only. See attachment A for the complete review.

Executive Summary:

The studies proposed by the sponsors do not completely address their stated study objectives. However, these studies may provide some insight about the comprehensibility of the label without measuring the extent of the problem. The limitations of their studies are as follows:

- The study population may not be representative of the targeted population.
- Conditions in which study populations are tested may not resemble real-life situations.
- Survey participants will be aware of study objectives.
- Questionnaire skip patterns may result in biased responses.
- There is not enough detail on the definition of "acceptable" responses.
- Sample size is not adequate to detect the label miscomprehension rate.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS reviewed the proposed Cipro (b) (4) container labels and carton labeling and have identified several areas of possible improvement, which might minimize potential user error.

1. DMETS does not recommend the use of the nomenclature (b) (4) for the following reasons:

   (b) (4) appears to be the most prominent name on the labeling inferring it is another proprietary name for the product and is misleading.

   ♦ The use of the (b) (4) nomenclature" is similar to that utilized by Pfizer for Zithromax Z-Pak. Health care providers prescribe Zithromax Z-Pak simply as (b) (4) OPDRA has safety concerns regarding the use of this unapproved nomenclature. (b) (4) is not an approved proprietary name and if a practitioner is unfamiliar with (b) (4) and attempts to find a reference to this name, they will be unsuccessful. Since (b) (4) is not an approved name, it does not exist in any reference text. OPDRA searched the PDR, Medline, Micromedex, Facts and Comparisons and American Drug Index for reference to (b) (4) and was unsuccessful.

2. The established name and expression of strength may need to be revised based on the outcome of the salt issue. In addition, 21 CFR 201.10 states "the established name shall be in letters that are at least ½ as large as the letters comprising the proprietary name and shall have a prominence with such proprietary name". We recommend the prominence of the established name be increased and revised to appear in the same font and appearance as Cipro (b) (4) n all labels and labeling.

3. Delete "Cipro (b) (4) which appears in red print.

4. Include the following on the principal display panel "ONCE DAILY".

5. Revise the Dosage section to read "Usual Dosage: One tablet daily for three days.".

6. A statement should be included as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed outpatient, it should be with a child-resistant container. For example:

   This unit-dose package is not child resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

   [Note: The second sentence is optional.]

7. The HOW SUPPLIED section of the insert labeling should be (b) (4)

8. The full text of the patient information section of the insert labeling should be reprinted at the end of the labeling to be in accordance with 21 CFR 201.57(f)(2).

9. We note the sponsor has proposed [redacted] (b) (4) We request the sponsor provide clarification.

IV. RECOMMENDATIONS

The Division of Drug Risk Evaluation has reviewed the proposed study protocols and determined the sponsor does not completely address their stated study objectives (see attachment A for complete review). The Division of Medication Errors and Technical Support does not recommend the use of the proprietary names [redacted] (b) (4)

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3242.

ATTACHMENT A

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 1, 2002

FROM: Parivash Nourjah, PhD
Division of Drug Risk Evaluation , HFD-430

THROUGH: Julie Beitz, MD
Division of Drug Risk Evaluation , HFD-430

TO: Jerry Phillips, R.Ph.
Division of Medical Errors and Technical Support, HFD-430

SUBJECT: Bayer study protocol review: [redacted] (b) (4) ™ Package Insert Comprehension/Package and Brand Name Assessment Study

PID# D010624,D010625

Executive Summary:

The studies proposed by the sponsors do not completely address their stated study objectives. However, these studies may provide some insight about the comprehensibility of the label without measuring the extent of the problem. The limitations of their studies are as follows:

- The study population may not be representative of the targeted population.
- Conditions in which study populations are tested may not resemble real-life situations.
- Survey participants will be aware of study objectives.
- Questionnaire skip patterns may result in biased responses.
- There is not enough detail on the definition of "acceptable" responses.
- Sample size is not adequate to detect the label miscomprehension rate.

Introduction:

This Memorandum is prepared in response to a request from the Division of Medical Errors and Technical Support to review the study protocol for package insert comprehension/package and brand name assessment submitted by Bayer Corporation. The products names are Cipro®UTI [redacted] (b) (4) ciprofloxacin 500 mg tablet) and [redacted] (b) (4) (extended release ciprofloxacin 500 mg tablet). Both studies have identical objectives except for the [redacted] (b) (4) protocol which includes an additional group (i.e. potential consumers for this product) for assessment of package insert comprehension.

This review will concentrate on the [redacted] (b) (4) protocol for Package Insert Comprehension/Package and Brand Name Assessment Study. However, these comments are also applicable for the Cipro [redacted] (b) (4) study protocol.

The [redacted] (b) (4) protocol includes the following objectives:

1. To evaluate physicians', pharmacists', and consumers' understanding of the draft [redacted] (b) (4) abeling (package insert) and how to safely prescribe, dispense, and use [redacted] (b) (4)

2. To measure how well physicians and pharmacists distinguish the [redacted] (b) (4) brand name and package from the conventional Cipro brand name and package.
3. To assess how pharmacists will differentiate [redacted] (b) (4) from the current Cipro products when viewing a mock physician prescription of the various currently prescribed Cipro regimens.

Study populations:

The protocol outlines a sample to consist of 200 physicians: 150 primary care physicians (family practitioners, general practitioners, internists, OB/GYNs) and 50 urologists; and 150 pharmacists. Both pharmacists and physicians are recruited over the telephone by using purchased lists of health care professionals as well as databases from approximately 12 marketing research sites.

Comments:

The sampling selection is a quota sampling. Since this is not a probability sampling, the response rate may not be calculated in the conventional manner. To better understand the response rate, the sponsor needs to keep a log of the number of telephone contacts, number of telephone contacts who agree to participate, and number of those who attend the testing sites. In my experience, the response rate will be quite low (i.e. 1% to 10%), therefore participants in this study may not be representative of the targeted population. Moreover, it is not clear what kind of sampling frame the sponsor is using (i.e., a list of physicians working for a specific HMO, American Physicians Association, or etc.)
It is also noteworthy to know where the locations of the 12 marketing research sites are in the United States. Are they geographically dispersed or mainly located in one or two regions in the U.S.?

The protocol outlines a sample of 150 female consumers who are 18 years or older from the general population and another 150 females from low literacy populations recruited from 6 shopping malls across the United States. Low literacy is defined as a reading skill at a maximum 7^{th}-8^{th} grade equivalency level.

Comments:

Type of sampling is convenience, thus those who participate in this study may not be representative of the typical users of this drug. The level of low literacy is still high. Approximately 20% of the U.S. adult population has a literacy level at or below 5^{th} grade but among elderly, this percentage is about 40% (Pfeiser Health Literacy Principal, 2^{nd} edition, 1989.) Given the indication of this drug, we recommend a level of literacy at a maximum 5^{th}-6^{th} grade equivalency level for low literacy consumers.

Method of data collection

Package insert comprehension assessment:

Physicians and pharmacists who agree to participate in the study will be invited to the marketing research sites for the interview. Physicians, pharmacists, and consumers will be asked to read package labels after they are briefed about the objective of the study. All the subjects can spend as much time as needed to read the label. During the questioning, both physicians and pharmacists can refer to the PDR or any other tool if they need to.

Comments:

The environment under which the subjects are interviewed may not be similar to real-life situations. For example, it is common for pharmacists to work under poor lighting and high background noise, which subsequently influence their comprehension.

Also, all subjects are aware of the objective of the study, which also may influence their reading and understanding of the labels. Another limitation of the data collection methodology is that the subjects could spend as much time reading the label as needed to understand it whereas in real-life the subjects may have limited time to read the label.

Assessment of differentiation of the (b) (4) brand name and package from conventional Cipro tablets:

In addressing Objective 3, mock physician prescriptions of the various currently prescribed cipro dosage forms are used.

Comments:

The sponsor does not provide a sample of mock physician prescriptions. Variations in handwriting should be included in this study.

Questionnaire design:

There are consistent skip patterns based on initial "correct" or "incorrect" answers.

For example as it is currently proposed, Question 4: Based on the package and drug label, should you prescribe this drug to treat a lower respiratory tract infection? The interviewer skips to question 5 if the subject's response is correct (i.e., NO.) However, if the subject's response was not correct (i.e., YES), the interviewer should ask: Why do you say that?

Comments:

Skip patterns may influence the subject's response. I recommend the follow-up question should be asked of all subjects regardless of whether their responses are correct or not.

Coding:

The questionnaire is pre-coded for the most part. In situations where there are verbatim responses, one coder creates codes based on 20% of the verbatim responses. Additional codes would be added as needed, and also more coders would be assigned if it becomes necessary. After the completion of the coding process, the final code sheet for each question will be sent to Bayer. (b) (4) and Bayer will work together to divide these codes into "correct," "acceptable," and "incorrect" responses.

Comments:
There are several issues with the coding process of verbatim responses. The verbatim comments are taken when the subject's answer is not the "correct" answer. For example, the physicians are asked "Based on the package and drug label, should you prescribe this drug to treat a complicated urinary tract infection?" If their response is not "NO", then the interviewer would ask "why do you say that? RECORD VERBATIM…"

My concerns about coding the verbatim responses are as follow:

1. The coding of the verbatim responses requires clinical knowledge; do coders have a clinical background?

2. Although using one coder results in consistency of the coding, it does not prevent systematic errors in coding. I recommend at least 2 coders to generate a consensual coding procedure.

3. Coders should be blinded to the objective of the study since it may influence their coding procedure. I recommend that the sponsor also submit the verbatim responses to FDA for review.

4. The list of "correct" and "acceptable" responses should be provided to FDA for review since there could be a disagreement between FDA and Bayer reviewers on the "acceptable" response.

Sample size:

The outcome measurement proposed for addressing the comprehension of label and packaging is based on the percent of correct responses (comprehension proportion). Although this measurement is equal to 1 minus percent of miscomprehension, it affects our interpretation of the study findings. Using this outcome measurement also leads to a different sample size requirement.

Using percent miscomprehension as an outcome measurement helps us to have a better feel for the extent of the problem. For example, if the percent of correct answers (i.e. proportion of comprehension) is computed to be 99%, it means 1% of respondents did not understand the label. Although 1% seems to be small and trivial, when it is applied to the overall targeted population, it results in a substantial number of misunderstanding events. For example, a misunderstanding percent of 1% in a population of 100,000 physicians means that 1000 physicians miscomprehend the label.

In calculating the sample size, when the point estimate is expected to be small, it is better to use relative precision rather than absolute precision. For example, the sample size needed to detect at least 1% miscomprehension should be sufficient to distinguish 1% from 0% miscomprehension. A sample size of 200 has an absolute precision of 1.3% and a 95% C.I of: -0.3% to 2.3%. Thus we could conclude erroneously that there is no problem with the label when there is indeed 1% misunderstanding. So, the sample size of 200 is not large enough to detect a 1% error with adequate precision. We suggest that the sample size be based on the relative precision of at least 30% of the point estimate. In that case, a sample size of 4200 is needed if one wants to detect a miscomprehension level of 1% with ± (30% of 1%).

The alternative approach to what I have suggested above is to use the lower bound of the 95% confidence interval for percent compreshension. For example if the percent comprehension is 99% (95% C.I.:97.7% - 100%), we should considered that the comprehenshion level can be as low as 97.7% and our policy toward label change should be based on this level.

Statistical Analysis

The sponsor would compute the number of and the percentage of "correct" and "acceptable," responses to each question. They propose that adequate label comprehension would be a summation of "correct" and "acceptable" responses.

It is important to know exactly what criteria the sponsor is using to determine the "acceptable" responses and the threshold at which the sponsor believes a change to the label is required.

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

/s/

Carol Holquist
3/27/02 12:21:43 PM
PHARMACIST

Jerry Phillips
3/27/02 12:29:41 PM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Associate Director, Medication Error Prevention
Office of Drug Safety, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:
Division of Special Pathogen and Immunologic Drug Products
HFD-590

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 29, 2002		21-473	NDA	July 18, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cipro XR	Standard review	Quinolone	August 31, 2002

NAME OF FIRM: Bayer

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Bayer submitted (b) (4) as their trade name with the NDA. This was reviewed and was found unacceptable. A meeting was held between the Agency and Bayer and the Agency requested a submission of a different trade name.
I'm attaching the cover letter to the consult. If you have any questions please contact Jouhayna Saliba or Susan Peacock at 72127.

PDUFA DATE: January 3, 2002
ATTACHMENTS: Draft Package Insert, Container and Carton Labels (these will be submitted once name is approved)
CC: Carol Holquist, Sammie Beam, Karen Lechter
Archival NDA 21-473
HFD-590 RPM Jouhayna Saliba and Susan Peacock
HFD-590 Reviewers and Team Leaders Rigoberto Roca, Maria Ruiz, Regina Alivisatos, Norman Schmuff, Dorota Matecka

SIGNATURE OF REQUESTER Jouhayna Saliba and Susan Peacock	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

July 18, 2002

Renata Albrecht, M.D., Acting 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 21-473
CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets)
General Correspondence – Change in Tradename

Dear Dr. Albrecht,

Bayer Corporation references the June 6, 2002 meeting held between Bayer and the Division concerning the review of NDA 21-473. During this meeting the Division and other Agency representatives expressed concern for the proposed tradename of the product – Cipro (b) (4) Bayer committed to revise the tradename based on these concerns and to quickly communicate a new name to the Division.

We also reference previous discussion with the Project Manager concerning a revision to the established or "generic" name for this product. Therefore, the name for this product is now formally proposed to be:

CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets)

Note that this was the name discussed briefly at the June 6 meeting, and was verbally endorsed by some of the Agency representatives in attendance. Please commence the review of this name as soon as possible. Bayer would like to be contacted immediately once this process has completed. Formal submissions of revised bottle labels and the package insert will be made at that time. 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, Pharm.D., Project Manager

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

7/29/02 10:28:36 AM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 29, 2002	**DUE DATE:** August 31, 2001	**ODS CONSULT #:** 01-0125-1

TO: Renata Albrect, M.D.
Acting Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH: Jouhayna Saliba
Project Manager
HFD-590

PRODUCT NAME: **Cipro XR** (Ciprofloxacin Hydrochloride and Ciprofloxacin Extended-Release Tablets) 500 mg **NDA #:** 21-473	**SPONSOR:** Bayer Corporation Pharmaceutical Division

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name "Cipro XR" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name Cipro XR.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-420; Parklawn Building Room 15B-32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 15, 2002

NDA NUMBER: 21-473

NAME OF DRUG: **Cipro XR**
(Ciprofloxacin Hydrochloride and Ciprofloxacin Extended-Release Tablets)
500 mg

NDA SPONSOR: Bayer Corporation Pharmaceutical Division

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogens and Immunologic Drug Products (HFD-590) for assessment of the proprietary name, *Cipro XR*.

The sponsor, Bayer Pharmaceuticals, previously proposed the proprietary names "Cipro (b) (4) and "Cipro (b) (4) for this drug product. On June 26, 2001, DMETS did not recommend the use of these names and also recommended that the sponsor consult with the CDER Labeling and Nomenclature Committee (LNC) with regard to the established name.

Subsequent to a meeting held on June 6, 2002 between the Division and the sponsor, the established name was revised to ciprofloxacin hydrochloride and ciprofloxacin extended-release tablets. In addition, the sponsor proposed the proprietary name Cipro XR.

PRODUCT INFORMATION

Cipro XR is the proposed proprietary name for ciprofloxacin hydrochloride and ciprofloxacin extended-release tablets. Cipro XR will be available as 500 mg tablets for once daily administration. Cipro XR indicated for the treatment of uncomplicated urinary tract infections caused by *Escherichia coli,* (b) (4) *, Proteus mirabilis, or Staphylococcus saprophyticus*. The usual dosage is 500 mg once daily for 3 days.

II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name “Cipro” has been utilized in the U.S. marketplace since June 1994. An Expert Panel discussion was conducted to address concerns with the use of the modifier “XR”. In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name “Cipro.”

A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name *Cipro XR*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not object to the modifier "XR", because "XR" has been commonly used for similar "extended-release" dosage forms marketed in the U.S. (e.g., *Tegretol XR, Voltaren XR, Dilacor XR, Glucophage XR,* and *Effexor XR).*

2. DDMAC did not object to the proprietary name Cipro XR in regard to promotional claims.

B. AERS DATABASE SEARCH

1. DMETS searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Cipro. The Meddra Preferred Term (PT), "Medication Error" and the drug names, "Cipro%," and "ciprofloxacin%", were used to perform the search.

   A total of 42 reports from the AERS search were retrieved and reviewed. Of the 42 reports reviewed, two accounts involved name confusion with Cipro (See Attachment I, Table 1).

2. DMETS also searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with "XR." The Meddra Preferred Term (PT), "Medication Error" and the drug names, "Adderall%", "Dilacor%", "Effexor %", "Glucophage%", "Tegretol%" and "Voltaren%" were used to perform the search.

   A total of 69 reports from the AERS search were retrieved and reviewed. Of the 69 reports reviewed, 7 accounts involved confusion with "XR" (See Attachment I, Table 2).

C. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has received two medication error reports involving name confusion with Cipro. One report involved a medication error between Cipro and Naproxen while another report involved a pharmacist dispensing Cipro tablets but labeling the bottle as generic Lortab 5 mg. Although Cipro products have been available since October 1987, only two medication error reports between Cipro and Naproxen and generic Lortab were received by the Agency. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Cipro, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Cipro.

Cipro XR contains the same active ingredient, Ciprofloxacin, as the currently marketed Cipro tablets. However, Cipro XR will be available as extended-release tablets. We recognize the need to differentiate the currently marketed Cipro tablets from this new product, Cipro XR; Cipro tablets are dosed twice daily while Cipro XR will be dosed once daily. DMETS does not object to the use of the modifier "XR" for this proposed product, since this is a common practice for similar "extended-release" dosage forms marketed in the U.S. (e.g., Tegretol XR™, Dilacor XR™, Glucophage XR™, Effexor XR™, and Adderall XR™). From the names listed above, all but Tegretol XR is dosed once daily; Tegretol XR is dosed twice daily. Based on the once a day dosing schedules, the modifier "XR" would be appropriate to identify the extended-release characteristic of Cipro XR.

According to a search in the Adverse Event Reporting System (AERS) for medication error reports with "XR", five medication error reports of confusion between Effexor and Effexor XR, one medication error report of confusion between Glucophage and Glucophage XR, and one medication error report of confusion between Adderall and Adderall XR were identified. In each case, the overlapping strength between the "non-extended release" and the "extended-release" formulations was the confounding factor that contributed to a medication error (See table 1). Overlapping strengths exist between the extended release and non-extended release formulations for Effexor XR/Effexor, Glucophage XR/Glucophage, and Adderall XR/Adderall.

Table 1

	Source AERS	Intended Product	Dispensed Product
1	3208763-8 (USP 52081)	Effexor XR 75 mg	Effexor 75 mg
2	3332283-3	Effexor 75 mg	Effexor XR 75 mg
3	3332288-2	Effexor 150 mg	Effexor XR 150 mg
4	3460522-7	Effexor XR 150 mg	Effexor 150 mg
5	3762570-6	Effexor 37.5 mg	Effexor XR 37.5 mg
6	3824270-3 (USP 54575)	Glucophage XR 500 mg	Glucophage 500 mg
7	3895548-2 (USP 54804)	Adderall XR 20 mg	Adderall 20 mg

In regards to Cipro and Cipro XR, a safety concern regarding the overlapping strength does exist. Cipro is available as 100 mg, 250 mg, 500 mg, and 750 mg tablets while Cipro XR will be available as 500 mg tablets. Therefore, we recommend careful monitoring and sufficient education regarding the difference between Cipro and Cipro XR tablets upon the launch of this product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Refer to ODS consult 01-0125.

IV. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name Cipro XR.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

_____

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment I

Table 1

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3760235-8	07/08/01	Cipro	Cipro 500 mg but mislabeled bottle as generic Lortab	A pharmacist dispensed Cipro 500 mg tablets to a patient and mislabeled the prescription container as being filled with hydrocodone/ASAP 5 mg/500 mg (generic Lortab).
2	3450729-7	02/03/00	Naproxen 500 mg	Cipro 500 mg	A prescription for Naproxen 500 mg tablets was incorrectly filled with Cipro 500 mg tablets.

Table 2

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3208763-8 (USP 52081)	2/10/99	Effexor XR 75 mg	Effexor 75 mg	Actual Error. A prescription for Effexor XR 75 mg was dispensed with Effexor 75 mg. The patient discovered the error prior to ingestion.
2	3332283-3	3/99	Effexor 75 mg	Effexor XR 75 mg	Actual Error. A patient received Effexor XR 75 mg instead of Effexor 75 mg. She experienced dizziness, diarrhea, and fell down without any muscle coordination.
3	3332288-2	5/4/99	Effexor 150 mg	Effexor XR 150 mg	Actual Error. A patient received Effexor XR 150 mg instead of Effexor 150 mg. She took Effexor XR 600 mg daily for an unknown amount of time.
4	3460522-7	4/13/99	Effexor XR 150 mg	Effexor 150 mg	Actual Error. A patient received Effexor 150 mg instead of Effexor XR 150 mg. Within a week of taking Effexor 300 mg daily, she experienced increased blood pressure.
5	3762570-6	6/11/01	Effexor 37.5 mg	Effexor XR 37.5 mg	Actual Error. A physician dispensed samples of Effexor XR 37.5 mg instead of Effexor 37.5 mg. The error was discovered prior to ingestion
6	3824270-3 (USP 54575)	10/25/01	Glucophage XR 500 mg	Glucophage 500 mg	Actual Error. A refill for Glucophage XR 500 mg was filled with Glucophage 500 mg. A patient discovered the error prior to ingestion.
7	3895548-2 (USP 54804)	3/12/02	Adderall XR 20 mg	Adderall 20 mg	Actual Error. A prescription for Adderall XR 20 mg was dispensed with Adderall 20 mg. The pharmacist did not realize that an extended release form of Adderall was available. The patient experienced no adverse outcome.

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/s/

Alina Mahmud
8/29/02 04:11:34 PM
PHARMACIST

Carol Holquist
8/29/02 04:25:58 PM
PHARMACIST

Jerry Phillips
8/31/02 08:55:54 AM
DIRECTOR

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2002

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 for additional clin/pharm information

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: December 6, 2002

TO: Andrew Verderame
Deputy Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172
FAX: 203-812-5029

FROM: Jouhayna Saliba

APPLICATION: NDA 21-473

SUBJECT: Request for additional information

We refer to your submission dated December 6, 2002, where you provided additional information to support certain labeling statements regarding renal insufficiency. We would like to thank you for providing that information and would like to request the following additional information:

- Please perform Monte-Carlo simulations of plasma ciprofloxacin concentration-time profiles in the following groups:

    1. Patients with severe renal impairment (CLcr < 30mL/min) given CIPRO XR 500 mg given once-daily for three days.

(b) (4)

- Please provide plots and a tabular list comparing the predicted daily peak and 24-hour exposures following these administrations.

- Please also provide your assumptions when conducting the above simulations.

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
12/12/02 11:53:19 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-473

Bayer Corporation Pharmaceutical Division
ATTN: Mr. Andrew S. Verderame
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	CIPRO® (b) (4) (ciprofloxacin hydrochloride and ciprofloxacin) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	March 4, 2002
Date of Receipt:	March 5, 2002
Our Reference Number:	NDA 21-473

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 4, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 3, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

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

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
4/22/02 06:26:07 PM
NDA 21-473

MEETING MINUTES

MEETING DATE: June 6, 2002
TIME: 1:00 p.m.
LOCATION: S400
NDA: 21-473
DRUG: Cipro (b) (4)
SPONSOR: Bayer
CONTACT NAME: Andrew Verderame
FAX NUMBER: 203-812-5029
PHONE NUMBER: 203-812-5172
PROJECT MANAGER: Jouhayna Saliba
DIVISION OF: Special Pathogen and Immunologic Drug Products, HFD-590
FORMAT: FACE TO FACE
TYPE of MEETING: B
MEETING REQUEST RECEIPT DATE: March 5, 2002
MEETING DATE CONVEYED TO SPONSOR: March 5, 2002 **VIA;** Telephone
BRIEFING DOCUMENT RECEIPT DATE: May 6, 2002 **ON TIME:** YES

FDA PARTICIPANTS, DIVISIONS, AND TITLES:

Renata Albrecht, M.D., Acting Division Director
Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Ruthanna Davi, M.S., Statistical Reviewer
Joette Meyer, Pharm.D., Clinical Pharmacology & Biopharmaceutics Reviewer
Carol Holquist, R.Ph., Office of Drug Safety
Ellen Frank, R.Ph., Chief, Project Management Staff
Andrew Cheung, pharmacy student
Jouhayna Saliba, Pharm. D., Project Manager

INDUSTRY PARTICIPANTS AND TITLES:

Mary E. Taylor, M.P.H.
Paul MacCarthy, M.D.
Lawrence Posner, M.D.
Deborah Church, M.D.

Daniel Haverstock, Ph.D
Steven Kowalsky, Pharm.D
Gabriele Fischer
John Lettieri, Ph.D.
Andrew Verderame
Robin Christoforides
Kamal Hamed, M.D.
Kathleen Gondek, Ph.D.
(b) (4)
Joseph Carofano
Tig Conger
Jonathan Harris, Ph.D.
Jennifer Stahl

BACKGROUND INFORMATION:

This meeting was requested by Bayer to discuss the trade name Cipro (b) (4) and to discuss the results and conclusions of the Cipro (b) (4) label comprehension study.

MEETING OBJECTIVES:

- Bayer will present the results and conclusion of the Cipro (b) (4) abel comprehension study
- Discussion between the Agency and Bayer with regard to the Cipro (b) (4) trade name
- Discussion of strategies to support the appropriate use of the product

QUESTIONS FOR DISCUSSION WITH RESPONSES AND DECISIONS REACHED:

1. We believe that the label comprehension study generated information that helped Bayer to identify labeling issues that had potential to cause confusion. We improved our package insert to enhance the understanding of the product and now expect increased assurance of the appropriate use of the product. Could the Division please comment?

   The Division commented that labeling modifications would be considered later during the review period of this NDA.

2. As per the discussions held prior to the NDA submission, we anticipate marketing this product in the US with the trade name ***Cipro*** (b) (4) Based on the outlined rationale, which is that this name most clearly supports and communicates the objective of appropriate use, does DSPIDP or the other invited Divisions have any comment on the name at this point?

   The Division along with the Office of Drug Safety strongly discouraged the inclusion of an indication in the trade name. Some concerns that were raised are the use of this name in hospital setting where standard medical abbreviations are used on prescriptions and can include the indication along with the trade name. Also, problems with verbal orders may

arise. Off label use maybe a problem also, since this product should be used for uncomplicated UTI.
The Division commented that the proposed new name may include the current Cipro prefix and the Division would consider an alternative suffix that refers to the kinetics of the alternative formulation, such as extended release.

3. We believe the label comprehension study supports that pharmacists can successfully differentiate the products. As stated previously, Bayer intends to package this product for distribution in bottles. Can the Division comment?

   The bottles will be an acceptable packaging option while Bayer looks at retesting and proposing an alternative trade name to the Cipro (b) (4) name.

4. Is the Agency in agreement that the proposed initial marketing and branding activities form the basis of an effective plan to adequately address concerns about potential off label use?

   The Division was encouraged with Bayer's educational plans and Bayer stated that they would also share their plans of an educational campaign for physicians, nurses or nurse practitioners. The Division encouraged Bayer to continue with their educational plans and have them submitted during the NDA review time so that the Division may offer comments or suggestions.

5. Within the development of this product, we have communicated and cooperated closely with the Division to address all requests received from FDA, including those made at the pre-phase III meeting and the pre-NDA meeting. We believe that we have provided everything that the Division needs to adjudicate on the uUTI NDA within the ten-month review cycle. Is there agreement on this point?

   The Division had no objection to a ten-month review cycle for the uUTI NDA.
   Bayer stated that the (b) (4) and the NDA will be submitted in October.
   The Division was in agreement with Bayer's proposal not (b) (4)

(b) (4)

ACTION ITEMS:

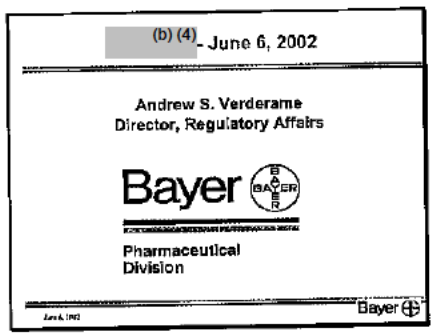
1. The Division will send Bayer details on the format of the electronic submission for the cUTI NDA.
2. (b) (4)
3. Bayer will share their plans with the Division for an educational campaign for physicians, nurses, and nurse practitioners.

Jouhayna Saliba, Pharm.D. Regulatory Project Manager
Minutes Preparer

Renata Albrecht, M.D., Acting Division Director
Meeting Chair

Attachment/Handouts: Overhead slides

Slide 1



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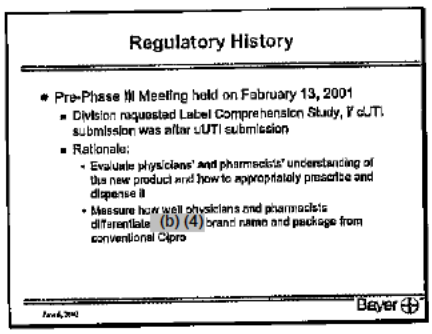

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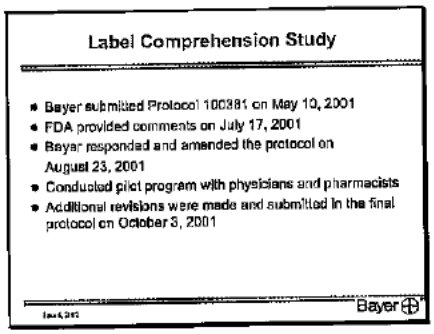

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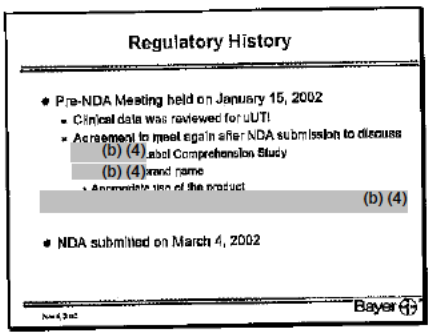

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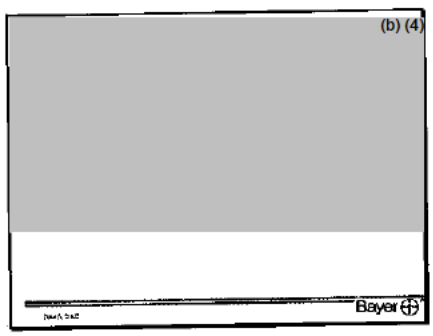

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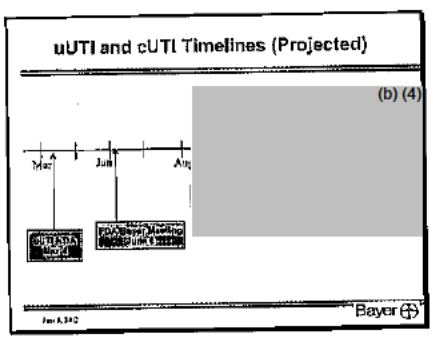

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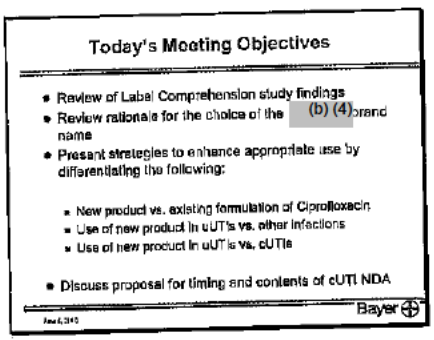

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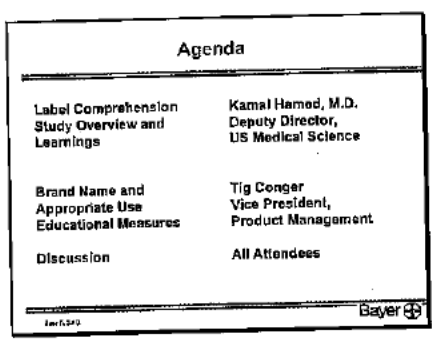

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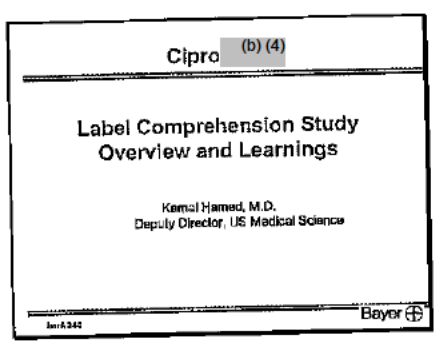

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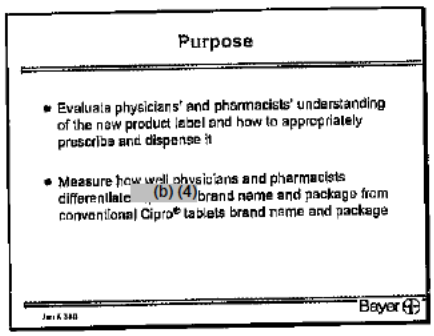

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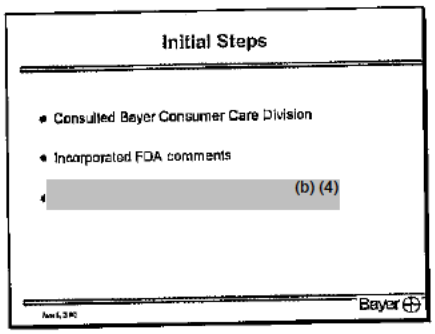

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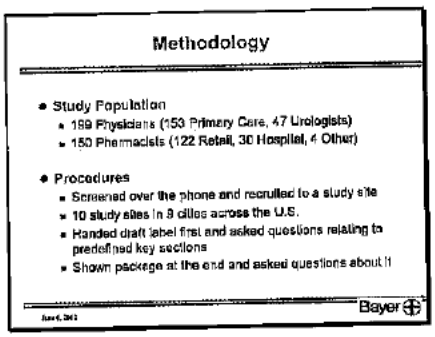

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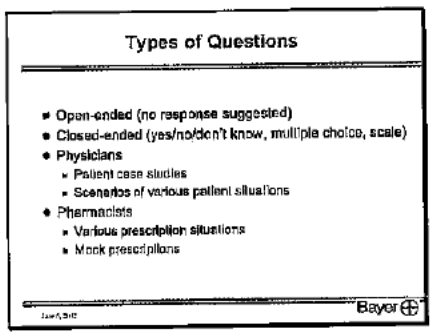

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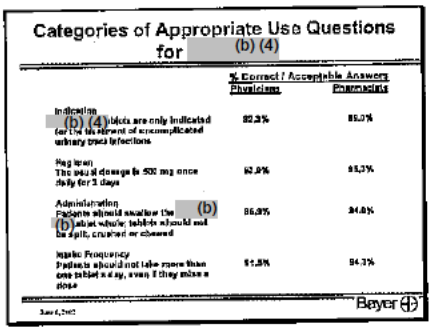

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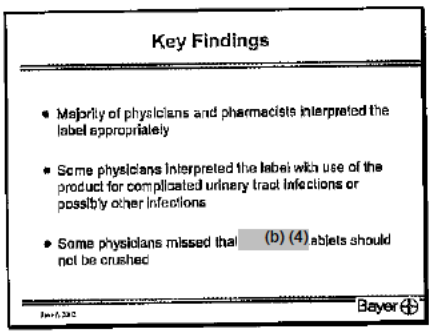

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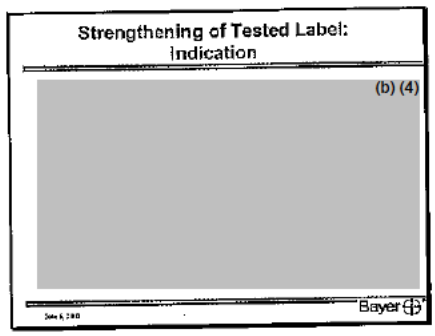

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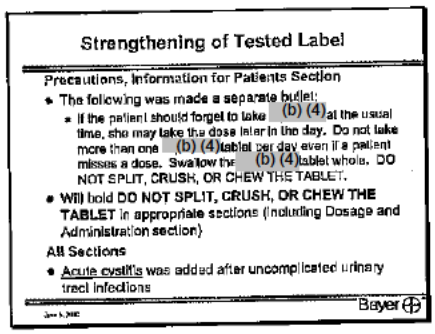

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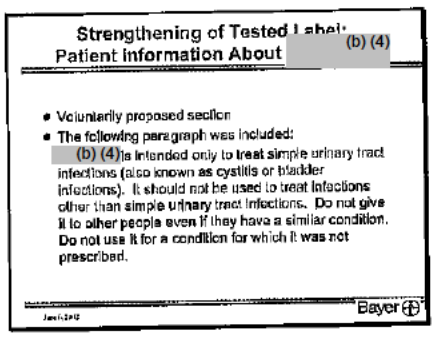

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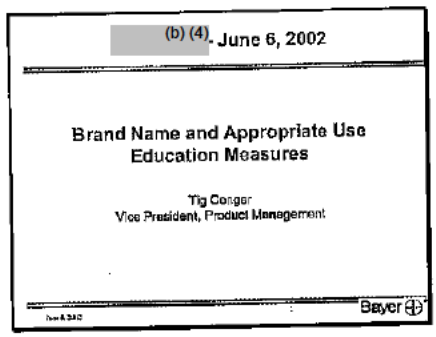

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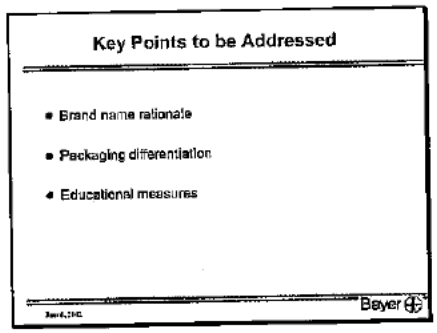

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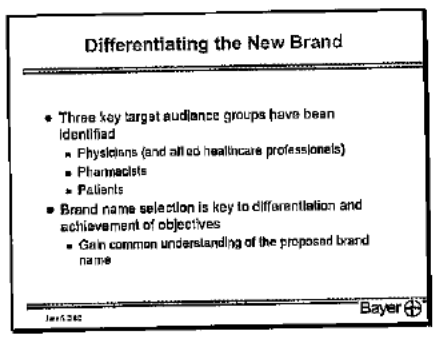

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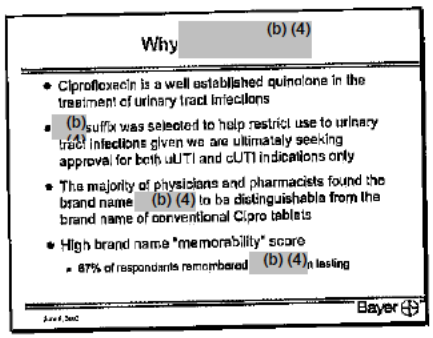

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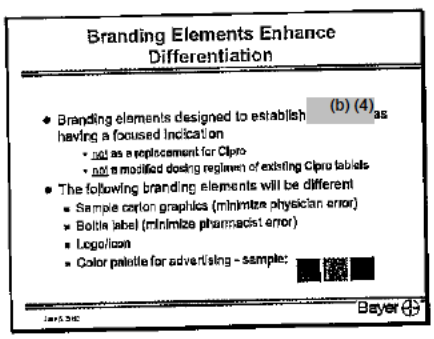

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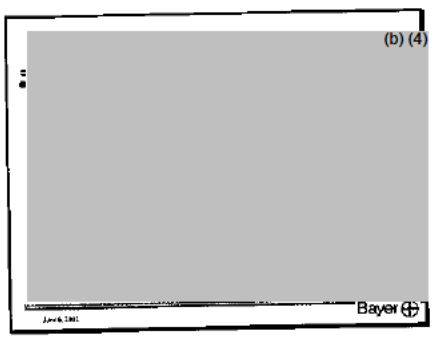

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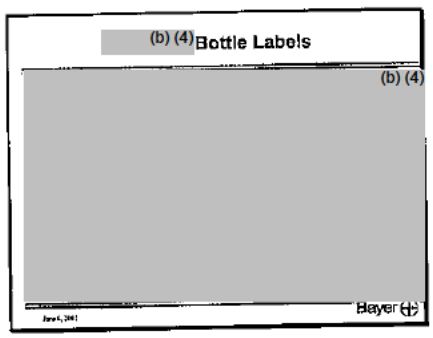

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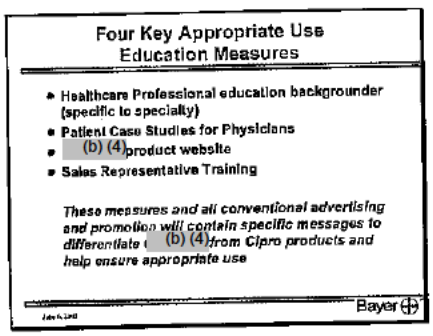

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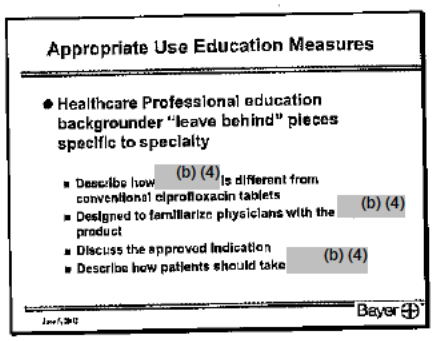

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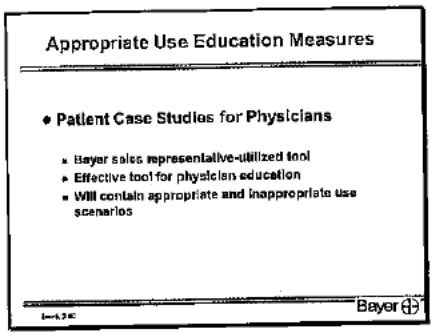

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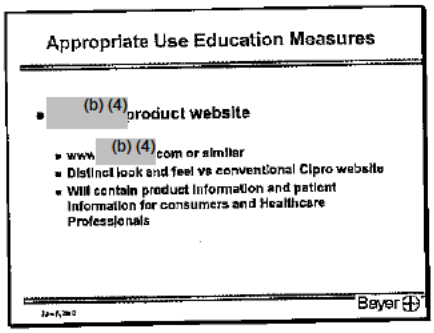

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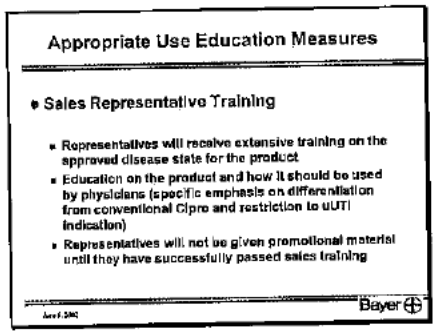

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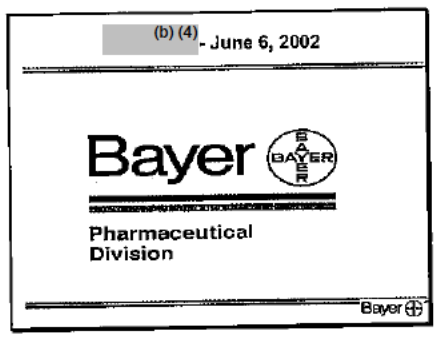

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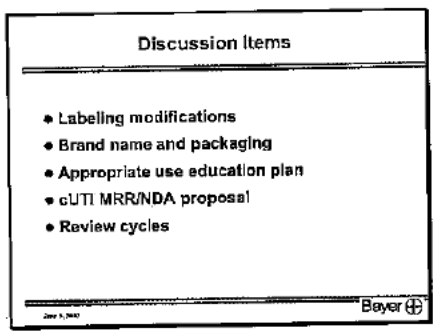

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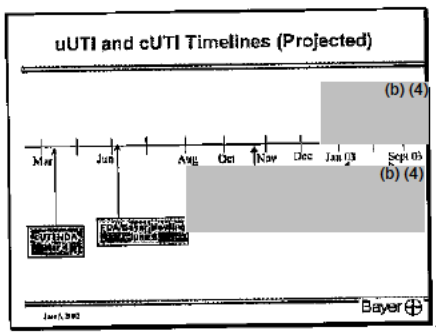

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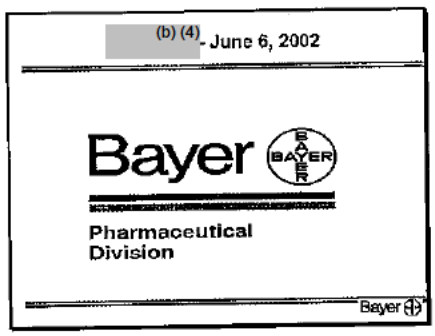

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/s/

Renata Albrecht
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Jouhayna Saliba
2/11/03 07:29:42 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF MEETING

DATE: February 15, 2002

MEETING TYPE: Pre-NDA CMC meeting

IND: 61,331

DRUG: Cipro [redacted] (b) (4)

BAYER ATTENDEES:
Shelina Bhojani, Associate Development Program, Regulatory Affairs
Gabrielle Fischer, Deputy Director, Project Management
Robin Christoforides, Assistant Director, Regulatory Affairs
Andrew Verderame, Deputy Director, Regulatory Affairs
Horst-Dieter Friedel, Quality Control Development
Maryann Graham, Quality Assurance Development
Andreas Ohm, Pharmaceutical Technology
Hans Scholl, Quality Assurance Development
Fritz Schueckler, Quality Control Development
Wolfgang Weber, Quality Control Development
Max Wegner, Global Regulatory Affairs

FDA ATTENDEES:
Norman Schmuff, Ph.D., Chemistry Team Leader
Dorota Matecka, Ph.D., Chemistry Reviewer
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Jouhayna Saliba, Pharm.D., Project Manager

BACKGROUND:
A meeting request for a teleconference dated December 6, 2001 was submitted by Bayer regarding IND 61,331. This meeting request was received by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) on December 7, 2001. This meeting is considered a Pre-NDA CMC meeting for the [redacted] (b) (4) of ciprofloxacin studied under IND 61,331. A background package for this Pre-NDA CMC teleconference was submitted January 18 and February 8, 2002.

Discussion items during this meeting are duplicated below. Division comments are duplicated below in italics.

Discussion Item (1)
As discussed with the Division during the End of Phase II CMC Teleconference, Bayer will submit 9 months of stability data on three primary stability batches of Ciprofolxacin [redacted] (b) (4)

Tablets 0.5 G. Stability studies will continue and Bayer will submit and update of the stability data for 52 weeks during the NDA review. Comparative dissolution data from embossed tablets will also be included in the NDA, as agreed during the End of Phase II CMC Teleconference.

The Division was in agreement with the above.

With regard to comparative dissolution, a bioequivalence study would not be required if the comparability of the products is demonstrated by dissolution profiles.

(b) (4)

Bayer questioned (b) (4)

Discussion Item (2)

As mentioned in Section 10, Stability, formation of trace amounts of (b) (4) (b) (4) was observed on tablets during long-term stability studies. Bayer is currently investigating the effect, which is considered a cosmetic defect that does not impact on efficacy and safety of the product. Bayer will provide additional information to the Division (no later than February 8, 2002) prior to the CMC Teleconference.

The Division had no comments

Discussion Item (3)

Because the active ingredient in Ciprofloxacin (b) (4) Tablets 0.5 G is a combination of two forms of Ciprofloxacin drug substance, Ciprofloxacin HCl, and ciprofloxacin (b) (4) (Ciprofloxacin betain), Bayer proposes to use "Ciprofloxacin" as the generic chemical name for the drug substance for all drug product labeling (e.g. package insert, bottle label). The proposed package insert (see Appendix 3 for an in-process draft PI) will contain a more detailed description of the two forms of ciprofloxacin.

Since the product contains both ciprofloxacin and ciprofloxacin HCl, the established name should include both names in order to comply with Section 501(b) of the Federal Food Drug and Cosmetic Act (the Act). Furthermore, in compliance with the Act, if either drug does not comply with the existing monograph, it should be clearly stated in the label in what specific regard it differs from the monograph. It was noted that this labeling requirement also applies to other ciprofloxacin products, and they should be revised to comply. .

Signature, minutes preparer: _____ Date: _____
Jouhayna Saliba, PharmD, Project Manager
Conference Chair (or designated signatory): _____ Date: _____
Norman Schmuff, Ph.D., Chemistry Team Leader

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/s/

Norman Schmuff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF MEETING

DATE: January 15, 2002

MEETING TYPE: Pre-NDA meeting

IND: 61,331

DRUG: Cipro (b) (4)

BAYER ATTENDEES:

Lawrence Posner, M.D., Senior Vice President, Pharmaceutical Development and Head of Worldwide Regulatory Affairs
Mary E. Taylor, MPH, Vice President, Regulatory Affairs
Deborah Church, M.D., Director Medical Affairs, Anti-Infective
Shelina Bhojani, Associate Development Program, Regulatory Affairs
Mark Kunkel, M.D., Director, Strategic Marketing, Anti-Infectives
Daniel Haverstock, Ph.D., Deputy Director, Statistics
Steven Kowalsky, Pharm.D., Global Clinical Project Leader, Global Project Management
John Lettieri, Ph.D., Deputy Director, Clinical Pharmacology
Barbara Painter, Ph.D., Deputy Director, Medical Affairs, Anti-Infectives
Kamal Hamed, M.D., Associate Director, Medical Affairs, Anti-Infectives
Gabrielle Fischer, Deputy Director, Project Management
Robin Christoforides, Assistant Director, Regulatory Affairs
Andrew Verderame, Deputy Director, Regulatory Affairs

FDA ATTENDEES:

Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Funmi Ajayi, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Karen Higgins, Ph.D., Statistical Team Leader
Ruthanna Davi, M.S., Statistical Reviewer
Kenneth Hastings, Ph.D., Pharm-Tox Team Leader

Stephen Hundley, Ph.D., Pharm-Tox Reviewer
Karen Lechter, J.D., Ph.D., Office of Drug Safety
Jouhayna Saliba, Pharm.D., Project Manager

BACKGROUND:
A meeting request for a Type B meeting dated November 14, 2001 was submitted by Bayer regarding IND 61,331. This meeting request was received by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) on November 16, 2001. Bayer sent a letter dated December 21, 2001 agreeing to a January 15, 2002 meeting date regarding this IND. This meeting is considered a Pre-NDA meeting for the (b) (4) formulation of ciprofloxacin studied under IND 61,331. A background package for this Pre-NDA meeting was submitted December 21, 2001.

Discussion items during this meeting are duplicated below. Division comments are duplicated below in italics.

Discussion Item (1)
As discussed with the Division during the End-of-Phase II meeting held on February 13, 2001, the Cipro (b) (4) NDA will contain one pivotal clinical study for the indication of uncomplicated urinary tract infections. In addition, the results from eight clinical pharmacology studies will also be submitted. Bayer has incorporated the Division's recommendations into the design of these studies. It is our intention to submit this NDA in March 2002.

The Division inquired about the format of the datasets for the pivotal clinical study, which will be submitted with the NDA. Bayer will submit the NDA electronically according to the Guidance. The Division requested an additional dataset containing one row of data per subject and including all variables used in the primary and secondary efficacy analyses. Bayer agreed to submit such a data set.

Discussion Item (2)
Two label comprehension studies were performed, one using "Cipro (b) (4), the other using "Cipro (b) (4) as the trade name. Data collection is completed and is being reviewed for analysis. Based on the results, Bayer may choose to revise the package insert or bottle labeling. In addition, Bayer will use these results in the development of the advertising and promotional materials.

The two label and package comprehension studies are completed and the data is being analyzed and will be included in the NDA. The analysis for these studies will be further discussed with the Division.

Discussion Item (3)
Bayer is also conducting (b) (4) (b) (4) The "Ongoing Clinical Studies" section in the uUTI NDA will contain safety information from the cUTI trial. We will also provide updated safety information for (b) (4) It is anticipated that a separate NDA for the 1 gram formulation will be submitted in October 2002.

The Division requested that periodic updates of the complicated UTI study be submitted to help make a decision on the uncomplicated UTI NDA. The Division inquired about the number of patients enrolled in the complicated UTI study. Bayer responded that approximately 475 patients are now enrolled and that the expected number of enrollment is 940 patients. Bayer told the Division that the (b) (4) (b) (4) *The Division also commented that the range of severity of patients in the complicated UTI study must include those patients in whom more severe disease is present to evaluate that off-label use in complicated UTI would be safe.*

Discussion Item (4) (b) (4) (b) (4)

Discussion Item (5)

The trade name for this product has not yet been finalized. It is Bayer's intention to choose a "Cipro" containing name for this product, such as "Cipro (b) (4) **or "Cipro** (b) (4) **or a Cipro-derivative of our choice.**

The trade name submitted will be discussed with the Division of Drug Marketing, Advertising and Communications (DDMAC) as well as, the Office of Drug Safety (ODS).

Additional comments:

(b) (4)

Signature, minutes preparer: _____ Date: _____
Jouhayna Saliba, Pharm.D., Project Manager

Conference Chair (or designated signatory): _____Date: _____
Rigoberto Roca, M.D., Medical Team Leader

Attachment/Handouts: Overhead slides

Introduction

- November 29, 2000 - Bayer submitted the Cipro (b) (4) IND
- February 13, 2001 - End of Phase II meeting
  - agreement on Clinical Pharmacology studies
  - agreement on one uUTI clinical study for submission of this indication
  - agreement on one cUTI clinical study for submission of cUTI indication (Division suggested 10% delta)
  - Division requested label comprehension study if uUTI was to be submitted before cUTI

Introduction

- March 1, 2001 - Division agrees with Bayer's proposal to submit separate NDAs for the 500 mg (uUTI) and 1 gram (cUTI) products
- May 17, 2001 - Division agrees that the preclinical sections of the Cipro (b) (4) NDA contain only a cross-reference statement to already-approved Cipro NDAs
- December 20, 2001 - NDA # 21-473 is assigned to the uUTI submission

Discussion Item # 5

- The trade name for this product has not yet been finalized. It is Bayer's intention to choose a "Cipro" containing name for this product, such as "Cipro (b) (4) or "Cipro (b) (4) or a Cipro-derivative of our choice.

January 15, 2002

Bayer

Discussion Item # 6

- Any items that the Division would like to discuss.

January 15, 2002

Bayer

Discussion Item # 3

- Bayer is also (b) (4) (b) (4) The "Ongoing Clinical Studies" section in the uUTI NDA will contain safety information from the cUTI trial. We will also provide updated safety information for cUTI in the 4-Month Safety Update. It is anticipated that a separate NDA for the 1 gram formulation will be submitted in October 2002.

Discussion Item # 4

- Bayer is currently conducting pediatric studies with the approved ciprofloxacin formulations (tablet, i.v., oral suspension). The development of a pediatric modified-release formulation is not feasible. We will be requesting a waiver for pediatric use information for this submission. It is our intention to include the relevant information gathered from the ongoing pediatric trials into the package insert for the once-daily product.

Discussion Item # 1

- As discussed with the Division during the End-of-Phase II meeting held on 2/13/01, the Cipro (b) (4) NDA will contain one pivotal clinical study for the indication of uUTI. In addition, the results from eight clinical pharmacology studies will be submitted. Bayer has incorporated the Division's recommendations into the designs of these studies. It is our intention to submit this NDA in March 2002.

Discussion Item # 2

- Two label comprehension studies were performed, one using "Cipro (b) (4) the other using "Cipro (b) (4) as the trade name. Data collection is completed and is being reviewed for analysis. Based on the results, (b) (4) (b) (4) In addition, Bayer will use these results in the development of the advertising and promotional materials.

Clinical Pharmacology - Drug Interaction Studies

- End-of-Phase II meeting February 13,2001
  - FDA request to complete 2 drug interaction studies
    - Proton pump inhibitor study
    - Antacid study

Bayer

Cipro (b) (4) - Results of Interaction Studies

- Omeprazole: 20% decrease in AUC when 1g Cipro (b) (4) was dosed with 40 mg omeprazole
- Maalox 70*: approximately 25% decrease in AUC when 1g Cipro (b) (4) was given 2 hours before, or 4 hours after 10 ml Maalox 70

*formulation not available in US

Bayer

Label Comprehension Study

- Study Population
  - Physicians (N = 200)
    - **PCPs (FPs, GPs, Internists, OB/GYNs)**
    - **Urologists**
  - Pharmacists (N = 150)
    - **Hospital**
    - **Independent retail pharmacy**
    - **Chain pharmacy**
    - **Other**
- Analysis plan
  - The questions asked both MDs and RPhs were incorporated into an overall test score (domain score)

January 15, 2002

Bayer

Format of Label Comprehension Report

Physician and Pharmacist Domain Scores

	Objectives	Physician Domain Scores (% Correct/Acceptable)
1	**Cipro (b) (4) ablets are indicated for the treatment of uncomplicated UTI**	(Average) (95%CI)
2	**The usual dosage is 500 mg once daily for three (3) days**	(Average) (95%CI)
3	**Patients should swallow the Cipro (b) (4) tablet whole; they should not split, crush or chew the tablet**	(Average) (95%CI)
4	**Patients should not take more than one (1) tablet a day, even if they miss a dose**	(Average) (95%CI)

January 15, 2002

Bayer

Conclusions (Study 100346)

- Efficacy
  - Cipro (b) (4) 500 mg QD was equivalent to the control regimen (conventional Cipro 250 mg BID)
- Safety
  - The adverse event profile was similar between Cipro (b) (4) 500 mg and conventional Cipro 250 mg BID

January 15, 2002

Bayer

Label Comprehension Study

- Objective
  - To evaluate physicians' and pharmacists' understanding of the Cipro (b) (4) labeling (PI) and how to safely prescribe or dispense Cipro (b) (4)
- Design
  - MDs & RPhs were asked to read the following sections of the PI for Cipro (b) (4)
    - **Indications**
    - **Dosage and Administration**
    - **Patient Information About Cipro (b) (4) Tablets**
  - Asked questions about the PI to determine their comprehension of the Cipro (b) (4) abel using:
    - **Patient case studies or scenarios**
    - **Scenarios for various patient prescription situations**

January 15, 2002

Bayer

100346: Response Rates (Population Valid for Efficacy)

Primary efficacy variable: rate of microbiological eradication at the Test-of-Cure visit

	Cipro (b) (4) 500 mg QD	Cipro 250 mg BID	95% CI
Bacteriological Response at TOC*	186/197 (94.4%)	205/219 (93.6%)	-3.5%, 5.2% (MH)
Clinical response at TOC**	187/197 (94.9%)	200/219 (91.3%)	-1.6%, 7.2% (MH)

* Eradication vs. Persistence + New Infection

** Cure vs. Failure

January 15, 2002

Bayer

100346 Overview of Safety Events

	Cipro (b) (4) 500 mg QD (N = 444)	Cipro 250 mg BID (N = 447)
Adverse Event (AE)	121 (27%)	105 (24%)
Serious AE	6 (1.4%)	6 (1.3%)
Discontinuation due to AE	2 (0.5%)	2 (0.4%)
Deaths	0	0

January 15, 2002

Bayer

Study 100346: Uncomplicated UTI

- Design: Prospective, randomized, double blind, comparative trial
- Countries: United States (58 centers)
- Study Regimens*
  - Ciprofloxacin Once Daily (b) (4) Tablet Arm
    - PO Cipro (b) (4) 500 mg QD
  - Conventional Ciprofloxacin Tablet Arm
    - PO Cipro 250 mg BID
- Duration of Therapy: short-course therapy (3 days)

*2-bottle system for blinding

January 15, 2002

Bayer

Study 100346: Patient Validity

	Cipro (b) (4) 500 mg (N = 452)	Cipro 250 mg BID (N = 453)
Valid for Safety	444 (98%)	447 (99%)
Valid for Efficacy	197 (43%)	219 (48%)

Most common reason for exclusion from efficacy population - " No causative organism isolated pre-Rx" (221 Cipro (b) (4) and 201 Cipro (b) (4)

January 15, 2002

Bayer

Ciprofloxacin Once Daily (b) (4) (b) (4) Tablet Development Program Pre-NDA Meeting

Steven F. Kowalsky, PharmD
Director,
Global Clinical Project Management, Anti-infectives
Bayer Corporation

Ciprofloxacin (b) (4) NDA Submission Package

The NDA submission (11/Mar/2002) will consist of:

- Single, pivotal Phase III clinical trial in uncomplicated urinary tract infection (Study 100346); plasma/urine samples incorporated as requested by FDA
- Label comprehension study
- Clinical Pharmacology program
  - Basic program: food effect studies, S-D and M-D pharmacokinetic studies compared to IR formulation
  - Drug interaction studies: antacid and omeprazole

Bayer

Pharmaceutical Division

January 15, 2002

Bayer

Ciprofloxacin (b) (4) Tablets

Agenda

Introduction :	***Andrew S. Verderame***
Clinical :	***Steven Kowalsky, Pharm.D.***
Discussion :	***All***

January 15, 2002

Bayer

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/s/

Rigoberto Roca
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MEMORANDUM OF MEETING

DATE:	May 2, 2001
MEETING TYPE:	End of Phase 2 Meeting
IND:	61,331
DRUG:	Cipro® (b) (4)
BAYER ATTENDEES:	Anja Dingler, Quality Control Development Horst-Dieter Friedel, Quality Control Development Fritz Scheuekler, Quality Control Development Wolfgang Weber, Quality Control Development Austin Bebyn, Pharmaceutical Technology Maryann Graham, Quality Assurance Kim Parthum, Quality Assurance Hans Scholl, Quality Assurance John Lettieri, PhD, Deputy Director, Clinical Pharmacology Gabriele Fischer, Associate Director, Project Management Robin Christoforides, Assistant Director, Regulatory Affairs Andrew Verderame, Deputy Director, Regulatory Affairs
FDA ATTENDEES:	Norman Schmuff, Ph.D., Chemistry Team Leader Joette Meyer, Pharm D, Clinical Pharmacology and Biopharmaceutics Reviewer Dorota Matecka, PhD, CMC Reviewer Jouhayna Saliba, R Ph, Project Manager

BACKGROUND: An End of Phase II teleconference meeting with Bayer to discuss their CMC plans for Cipro® (b) (4)

Discussion Items:

1. Bayer plans to submit 9 months of stability data on three primary stability batches for Cipro® (b) (4) Tablets, 0.5 g and 1.0 g. Stability studies will continue and Bayer commits to provide updated stability reports upon request.

   The Division asked for clarification on the nine months stability data being submitted for Cipro® (b) (4) Tablets, 0.5g and 1.0g.

   Bayer plans to submit the nine months stability data for the 500mg tablets under the uncomplicated UTI indication and the 1.0g stability data under the complicated UTI indication. Bayer will provide the updated stability reports without the Division's request.

2. The Primary stability data to be included in the future NDA are being generated on tablets without embossing and without printing. Product for the market will most likely be embossed with a unique identity mark. Based on the retardation principle of Cipro® (b) (4) tablets (as discussed in the briefing summary in section 3), Bayer considers this change minor, which would be covered by providing data from the first production batches for the commercial product with unique identity markings. Therefore, Bayer believes a bioequivalence study is not required and equivalency between the tablets with and without embossing will be demonstrated by in vitro dissolution testing.

   The Division is in agreement that a bioequivalence study is not required. In addition, we agree to the proposal for in vitro dissolution testing between the tablets with or without embossing. The Division also requested that full dissolution profiles using the F_2 similarity factor be submitted.

3. *The Division inquired about the dates of when the NDAs will be submitted.*

   Bayer will be submitting the NDA for the uncomplicated UTI by December 2001 (b) (4)

   (b) (4)

Signature, minutes preparer: _____ **Date:** _____
Jouhayna Saliba R.ph., Project Manager

Conference Chair (or designated signatory): _____ **Date:** _____
Norman Schmuff, Ph.D., Chemistry Team Leader

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/s/

Norman Schmuff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF MEETING

DATE: February 13, 2001

MEETING TYPE: End of Phase 2 Meeting

IND: 61,331

DRUG: Cipro (b) (4)

BAYER ATTENDEES:

Carl Calcagni, R.Ph., Vice President, Regulatory Affairs
Paul MacCarthy, M.D., Vice President, Medical Affairs
Deborah Church, M.D., Director Anti-Infective Medical Affairs
Steven Kowalsky, Pharm.D., Ciprofloxacin Global Clinical Project Leader
Pavur Sundaresan, M.D., Director, Clinical Pharmacology
John Lettieri, Ph.D., Deputy Director, Clinical Pharmacology
Barbara Painter, Ph.D., Microbiology
Gabrielle Fischer, Project Management
Kim Parthum, Ph.D., Quality Assurance
Robin Christoforides, Regulatory
Andrew Verderame, Regulatory
John Warner, Statistics
Heino Stass, Ph.D., Clin. Pharmacology, Bayer Germany
Hans Diter Freidl, Ph.D., Chemistry, Bayer Germany

FDA ATTENDEES:

Mark Goldberger, M.D., M.P.H., Division Director, DSPIDP
Renata Albrecht, M.D., Deputy Director, DSPIDP
Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Funmi Ajayi, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Karen Higgins, Ph.D., Statistical Team Leader
Ruthanna Davi, Ph.D., Statistical Reviewer
Stephen Hundley, Ph.D., Pharm-Tox Reviewer

Shukal Bala, Ph.D., Microbiology Team Leader
Dorota Matecka, Ph.D., CMC Reviewer
Rosemary Johann-Liang, M.D., Medical Reviewer
Fonda Chen, Pharm.D., Clin. Pharm.& Biopharm Fellow
Valerie Jensen, R.Ph., Project Manager

BACKGROUND:
A meeting request for a Type B meeting dated November 28, 2000 was submitted by Bayer regarding IND 61,331. This meeting request was received by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) on November 29, 2000. Bayer sent a letter dated December 5, 2000 agreeing to a February 13, 2001 meeting date regarding this IND. This meeting is considered an End of Phase 2 meeting for the (b) (4) formulation of ciprofloxacin studied under IND 61,331. A background package for this End of Phase 2 meeting was submitted January 23, 2001.

Discussion items during this meeting are duplicated below. Division comments are duplicated below in italics.

Discussion Item (1)
Since CIPRO (b) (4) is bioequivalent in terms of AUC and the PK/PD parameters (e.g. AUIC and C_{max}/MIC) appear acceptable to achieve satisfactory efficacy and safety, then clinical pharmacology studies may be sufficient for approval of all urinary tract indications (including chronic bacterial prostatitis) without a need for large scale Phase III studies.

The Division stated that rate and extent of absorption are the required criteria for bioequivalence and that the trough (C_{min}) is an important consideration for antiinfective indications. The Division pointed out that although the AUCs of the (b) (4) ciprofloxacin and the (b) (4) ciprofloxacin (b) (4) are comparable, there is a significant difference in the concentration at the end of the dosing interval which may be of clinical importance. Also the implications for clinical efficacy of a second peak concentration during a twenty-four hour period (as is obtained with the (b) (4) formulation dosed twice daily and is not obtained with the (b) (4) formulation) are unknown.

Bayer raised the issue of intravenous (IV) ciprofloxacin (the IV formulations were approved in 1990) being approved based solely on the fact that it demonstrated a comparable extent of systemic absorption (i.e., AUC) to the oral (IR) formulation.

The Division stated that 1) the pharmacokinetic profiles are comparable with the exception of a slight increase in C_{max} (which was considered not to pose a safety concern), and 2) the regimens for both the IV and oral (b) (4) ciprofloxacin formulations are the same. The Division has not found a precedent where a new formulation was approved based on bioequivalence to an approved formulation when the dosing frequency of the new formulation is not the same as the already approved formulation. Approvals for (b) (4) formulations have in the past always relied on clinical confirmation of efficacy. The Division will require clinical data to confirm efficacy for the (b) (4) formulation of ciprofloxacin.

Discussion Item (2)
Pharmacokinetic data from conventional CIPRO Tablets are considered to be relevant to special patient populations such as the renally impared, hepatically impaired, and elderly. Therefore, no additional special population PK studies are planned.

The Division agreed with Bayer's plan but asked for an interactions study with antacids due to the broader absorption window seen with the MR formulation.

Bayer agrees to perform an antacids study with this formulation.

The Division stated that the need for an interaction study involving proton pump inhibitors will be evaluated after review of literature information and/or data from Bayer.

Discussion Item (3)
If the Agency disagrees with item (1), Bayer would propose that a single clinical trial in both uncomplicated and (b) (4) safety and efficacy data to support approval (b) (4)

Bayer proposes submitting the NDA for the 500 mg (b) (4) tablet for uncomplicated UTI (uUTI) in December 2001 and (b) (4) (b) (4)

The Division commented that the cUTI data will be valuable in the decision to (b) (4) The Division stated that the Division (b) (4) The Division agreed to explore options, including the possibility of (b) (4) to administratively handle (b) (4)

Discussion Item (4)
Bayer stated that the (b) (4) formulation will have a separate label (PI) from the already approved ciprofloxacin formulations.

Discussion Item (5)
As per the Statistical Considerations in the Guidance Document entitled, "Complicated Urinary Tract Infections and Pyelonephritis", a delta of 15% would be used.

The Division stated that there would be concerns if the (b) (4) formulation had a lower cure rate than the (b) (4) formulation and the lower limit of the 95% confidence interval of the difference was between 10-15%. The Division recommended that if Bayer thinks the lower limit will be close to 15%, they may want to consider increasing the sample size.

Discussion Item (6)
A labeling comprehension study would not be necessary for approval in light of:

- **Bioequivalent AUC**
- **Serum concentrations that are unlikely to be influenced by posture or ranitidine**

- **Potential off-label use would not pose an undue safety concern**
- **Bayer's plan to label the product appropriately for use only in UTI**

The Division stated concerns regarding a situation where the uncomplicated UTI indication may be approved before (b) (4) *indication and there would be the risk of a physician prescribing this formulation for* (b) (4) *indication before the product has been approved* (b) (4) *The Division would request a physician labeling comprehension study if the* (b) (4) *will not be approved at the same time as the uUTI indication. A labeling comprehension study is also requested by the Division in order to decrease the risk of this* (b) (4) *formulation being* (b) (4) (b) (4)

Once Bayer has draft labeling and a proposed name and packaging for this product, the Division requests that these be submitted so that the Office of Post MarketingDrug Risk Assessment can be consulted. The Division discussed with Bayer what we meant by a "labeling comprehension study" and stated that this type of study would involve the proposed package and package insert and may involve focus groups of physicians and pharmacists to see if they understand the product's labeling. A pharmacist portion of this study may involve product name recognition and the assessment of whether a pharmacist realizes from a mock prescription for the (b) (4) *formulation that the* (b) (4) *ciprofloxacin is a different formulation from conventional ciprofloxacin tablets. Such a study may also involve case studies which would test physicians' comprehension of what the* (b) (4) *product is labeled for and assess the likelihood of whether a physician would use the product off-label after reading the product's proposed label.*

Discussion Item (7)
Bayer proposed (b) (4)

Signature, minutes preparer: _____ Date: _____

Conference Chair (or designated signatory): _____ Date: _____
Attachment/Handouts:
Overhead slides

/s/

Mark Goldberger
3/1/01 03:08:36 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-473 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: March 5, 2002 Action Date: December 13, 2002

HFD-590 Trade and generic names/dosage form: CIPRO® XR (ciprofloxacin extended release tablets)

Applicant: Bayer 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): 1

Indication #1: Uncomplicated 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): December 31, 2008

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: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____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:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**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**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **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.

ction 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}

_____
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
2/10/03 03:08:24 PM

Pediatric Studies Waiver Request

Pursuant to 21 CFR 314.55 (c), Bayer Corporation Pharmaceutical Division requests a full waiver of the assessment of the efficacy and safety of Cipro (b) (4) 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. Definitive statements concerning if this effect manifests itself in human pathology cannot be made presently. Ongoing ciprofloxacin trials (reference Ciprofloxacin Oral Suspension IND 43,007) being conducted by Bayer should provide additional information on this subject. It is anticipated that Bayer will report the results of these studies to the Division in September, 2003.

Ciprofloxacin is an extremely bitter drug substance. (b) (4)

(b) (4)

Therefore, Bayer requests a full waiver for the assessment in pediatric patients for this NDA. We do commit, however, to include the relevant information gained from the ongoing studies being conducted under IND 43,007 in the Cipro (b) (4) package insert.