CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-473

MEDICAL REVIEW(S)

MOR 21-473
CIPRO XR (formerly known as Cipro— and Cipro -

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

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,* — *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,* — *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 — The 500 mg tablet is intended for the treatment of uncomplicated urinary tract infections (the subject indication of this NDA) and the —

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® 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® 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® 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® 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® — 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 — and Cipro —

Indication: Ciprofloxacin XR 500 mg tablets are indicated in the treatment of uncomplicated urinary tract infection (acute cystitis) caused by *Escherichia coli*, —————, *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® — (proposed)

Pharmacologic Category: Fluoroquinolone

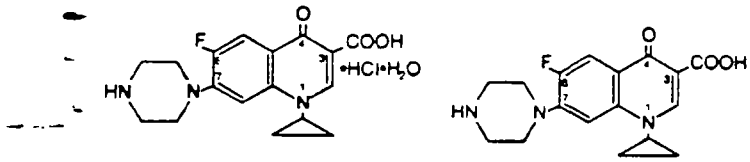
Chemical Name: The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base).

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, 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:

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 [redacted] (ciprofloxacin equivalent) strengths. The 500 mg tablet is intended for the treatment of uncomplicated urinary tract infections (the subject indication of this NDA)

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".

[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 [redacted] indication in conjunction with one uncomplicated UTI trial. In this case pathogens listed in the [redacted] 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 [redacted]

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.

[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®	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:
  Tablets submitted (protocol 100346 included)
- February 13, 2001: End of Phase II meeting:

The results of the Phase I studies of the versus IR tablets, and subsequent PK/PD calculations were presented. The FDA had concerns that the 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 trail for t. 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

.. An agreement was reached on 3/1/01 that 2 separate NDAs for the uncomplicated UTI and ; 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 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 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

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 ——— 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 ——— exhibits dissolution characteristics aimed to deliver the equivalent exposure to drug as the corresponding conventional ciprofloxacin tablet (Cipro®) ——— 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: [redacted]

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 [redacted]

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® — group. To determine whether the Cipro XR group

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

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

Table 3
Reasons for premature discontinuation of treatment

	Cipro XR (N=452)	Cipro® (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® group did not receive study medication. All 8 from the Cipro XR group and 6 from the group were excluded from the safety population. 1 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® 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®
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®		
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® group received other antimicrobial agents before the TOC.

Table 6
Reasons for exclusion from efficacy analysis

	Cipro XR (N=452)	Cipro® (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® — 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® — (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® — 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® — subjects received previous antimicrobials including levofloxacin, Flagyl, TMP and TMP/SMX.

5 Cipro XR subjects and 3 Cipro® — 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 — (N = 199)	Cipro® — (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® — 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® — group. The 2 pools of small centers combined had eradication rates of 100% in the Cipro —: group and 91% in the Cipro® — group.

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

Center	Cipro XR N/N	Cipro® 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® 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® — was numerically superior versus Staphylococcus saprophyticus and Proteus mirabilis.

A new infecting organism was identified in 3 Cipro XR subjects and 4 Cipro® — 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® — 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® (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® 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®
	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® 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® arm and 3 on the Cipro XR arm. 2 Cipro XR subjects and 5 Cipro® 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® arm.

Clinical response:

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

Clinical Cure	Cipro XR	Cipro®	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® 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® at both timepoints.

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

Post therapy antimicrobial agents were used by 25 (13%) Cipro XR patients and 28 (13%) Cipro® 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® 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®	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® 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® 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® —patients with similar outcomes.

Table 15
Patients with *Staphylococcus saprophyticus* at >10^4 and <10^5 Pre-Therapy

	Cipro XR	Cipro® —
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® — as well as 1 additional Cipro XR and 2 additional Cipro® — subjects with counts >10^4 for a total of 7 Cipro XR and 9 Cipro® — subjects. As noted above for —— 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® —) 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® — 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® — 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® 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® — 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 —— 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 — vs. IR)	500 mg — 500 mg — 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 — 1000 mg —	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 — 500 mg	500 mg Fasted 500 mg Fed (High-Fat, High-Calorie)	Once Once
Study 10339	12	3-Way Cross-Over, Randomized, Unblinded — vs. IR)	1000 mg — 1000 mg — 500 mg IR	1000 mg Fasted 1000 mg Fed 1000 mg Fasted	Once Once Once
Multiple Dose					
Study 10324	19	Cross-Over, Randomized, Unblinded — vs. IR)	1000 mg — 500 mg IR	1000 mg QD 500 mg BID	5 days 5 days
Study 10325	19	Cross-Over, Randomized, Unblinded — vs. IR)	500 mg — 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 —	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 —	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 ___ ; QD versus Cipro® ___ 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 ___mg PO QD Cipro® 500 mg PO BID	7-14 days 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® — 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 — 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® — Of these 453 patients, 6 did not receive study drug. Thus, there were 447 (99%) patients evaluable for safety in the Cipro® — 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® — 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® — 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® — 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®	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®	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® 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® 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® 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® 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® — 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® — 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® — 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® 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® 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® 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® arm. 12/444 (3%) of Cipro XR and 15/447 (3%) of Cipro® 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® 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® 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® —— 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® — 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® — 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® — 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® — remained unchanged. Included were 1 severe AE on the Cipro XR arm (accidental on-the-job injury) and 3 severe AEs in the Cipro® —— 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® — 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® — 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® — 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® —— 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® — 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® 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® 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® 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® 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® group. 7/13 SAEs were unintended pregnancies (3 in the Cipro XR group and 4 in the Cipro® 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® —), 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® — 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®	
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 — mg tablets.

The overall incidence rate for any event was 24% for the Cipro XR 500 mg tablet and 18% for the Cipro XR — 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 — 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 — 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 — 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® —, 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® — 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® —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® — 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® — 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® —), 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® — 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® — 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® group. 7/13 SAEs were unintended pregnancies (3 in the Cipro XR group and 4 in the Cipro® 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® 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
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9/13/02

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

Indication: Ciprofloxacin XR 500 mg tablets are indicated in the treatment of uncomplicated urinary tract infection (acute cystitis) caused by *Escherichia coli*, —, *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 — 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 — mg tablets in the treatment of —

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 — mg tablets in —

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

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,* —— *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® — 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® — 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® — 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® — 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® — patients with similar colony counts and outcomes added to the dataset.

Of great weight in the decision making process was the fact that ciprofloxacin immediate release has already been granted an approval for *Staphylococcus saprophyticus*. Both Cipro XR and Cipro — 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.

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.

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 — 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 — The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO XR minus Cipro — 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
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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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