CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-473

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

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

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

EXECUTIVE SUMMARY

The applicant is seeking approval of CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin*) tablets containing ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration in NDA 21-473. CIPRO® XR Tablets (sometimes referred to as Ciprofloxacin tablets) are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The proposed indications are treatment of uncomplicated urinary tract infections caused by aerobic gram-positive such as *Enterococcus faecalis, Staphylococcus saprophyticus* and gram-negative microorganisms such as *Escherichia coli,* , *Proteus mirabilis.*

CIPRO® XR is a new modified release once-daily (OD) new tablet formulation of ciprofloxacin with a rapid onset of action. Ciprofloxacin is bactericidal at concentrations only two to fourfold above its bacteriostatic concentrations. Its bactericidal action results from inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, which are enzymes required for bacterial DNA replication, transcription, repair and recombination.

CIPRO® XR tablets are coated, two-layer tablets containing both immediate- release and controlled-release components. Approximately 35% of the dose is provided by the immediate-release component and 65% by the slow-release matrix. The tablets contain both ciprofloxacin hydrochloride and ciprofloxacin betaine (base), and excipients that contribute to the desired characteristics of the formulation.

Eight clinical pharmacology studies were conducted with CIPRO® XR, 3 with the 500 mg tablet, and 5 with the 1000 mg tablet. (Data from the studies on the

. All studies were conducted in healthy young male volunteers. These studies compared the ciprofloxacin pharmacokinetics of

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

The 24-hour area under the curve (AUC) obtained following administration of 500 mg CIPRO® XR was shown to be equivalent to that attained with BID dosing of 250 mg immediate release ciprofloxacin. The bioavailability of the — tablet was not altered by administration with food (either a high-fat or a low-fat meal), and did not change upon multiple dosing for 5 days. The C_{max} achieved following administration of the 500 mg — tablet is higher than that observed for the 250 mg immediate release tablet, but lower than the C_{max} expected from a 500 mg immediate release tablet. Trough plasma concentrations are lower with the 500 mg — once-daily regimen compared to the 250 mg BID regimen. However, urine concentrations of ciprofloxacin following dosing with 500 mg CIPRO® XR are maintained well above (>100-fold) the *in vitro* MIC_{90} for *Escherichia coli* (about 0.03 µg/mL).

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

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

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in original NDA 21-473 for CIPRO® XR. The Human Pharmacokinetics and Bioavailability Section of NDA 21-473 has met the requirements of the 21 CFR 320 and the clinical pharmacology labeling requirements of 21 CFR 201.56.

Dissolution: Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method for the tablet (USP Apparatus 2, rotation speed of 50 rpm, and dissolution medium of 0.1N HCl), is acceptable. Specifications should be as follows:

30 minutes:
60 minutes:
120 minutes:

Labeling: The proposed label for ciprofloxacin tablets is attached.

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

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

APPEARS THIS WAY ON ORIGINAL

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SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Single-dose and steady-state pharmacokinetics of CIPRO 500 mg — tablet vs. IR tablet

The applicant studied the single dose and steady state pharmacokinetics of a newly developed oral 500 mg ciprofloxacin once daily tablet given to healthy subjects after an overnight fast according to a once daily dosing regimen for five days. In addition a comparison to the standard immediate treatment regimen (250 mg immediate release given bid) was performed. The pharmacokinetic parameters determined were: maximum plasma concentration (C_{max}), maximum plasma concentration (C_{maxss}) at steady state, time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration versus time (AUC) curve, area under the plasma concentration versus time (AUC_{0-24}) curve for 0-24 hours, area under the plasma concentration versus time (AUC_{0-24ss}) curve for 0-24 hours at steady state, area under the plasma concentration curve versus infinite time (AUC_{inf}), amount excreted in urine (Ae_{ur}). The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new CIPRO 500 mg — formulation to healthy male subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation.

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

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

Effect of a high calorie, high fat meal on the pharmacokinetics of ciprofloxacin 500 mg — tablet

The applicant evaluated the effect of a high calorie, high fat meal (250 mL whole milk, 2 slices toast, 2 scrambles eggs, 3 slices fried ham, 125g hash brown potatoes, 20g butter and 2 cups decaffeinated coffee- providing a total of 977 Kcal) on the pharmacokinetics of CIPRO 500 mg — formulation in healthy subjects. The 500 mg Ciprofloxacin — formulation was found to be bioequivalent when administered under fasted and high fat, high calorie fed conditions. Hence, food does not appear to affect the rate or extent of ciprofloxacin exposure.

Effect of —— on the pharmacokinetics of ciprofloxacin 500 mg —tablet

The applicant determined the influence of co-administration of the antacid —— on ciprofloxacin pharmacokinetics when a single 1000 mg dose of the ciprofloxacin

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

Effect of Omeprazole on the pharmacokinetics of ciprofloxacin 500 mg — tablet

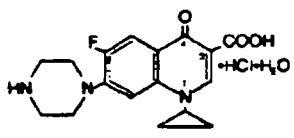
The applicant determined the influence of a three day 40 mg omeprazole pretreatment on the pharmacokinetics of ciprofloxacin administered orally as a 1000 mg dose of the ciprofloxacin —tablet 2 hours after a dose of 40 mg omeprazole. The exposure of ciprofloxacin was decreased (<20%) by pre-treatment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

QUESTION BASED REVIEW

General Attributes

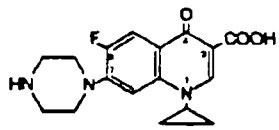
What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

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



Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7- (1- piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight

It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



The composition of the commercial tablet formulation is as follows:

Ingredient	Amount (mg/tablet)
IR -Laver	
Ciprofloxacin hydrochloride	
Crospovidone	
Magnesium stearate	
Silica colloidal anhydrous	
CR -Laver	
Ciprofloxacin hydrochloride	
Succinic acid	
Hypromellose	
Magnesium stearate	
Silica colloidal anhydrous	
Film Coat	
Hypromellose	
Polyethylene glycol	
Titanium dioxide	
Total Weight	

What is the proposed mechanism of drug action and therapeutic indications?

Ciprofloxacin is bactericidal at concentrations only two to fourfold above its bacteriostatic concentrations. Its bactericidal action results from inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, which are enzymes required for bacterial DNA replication, transcription, repair, and recombination.

What is the proposed dosage and route of administration?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

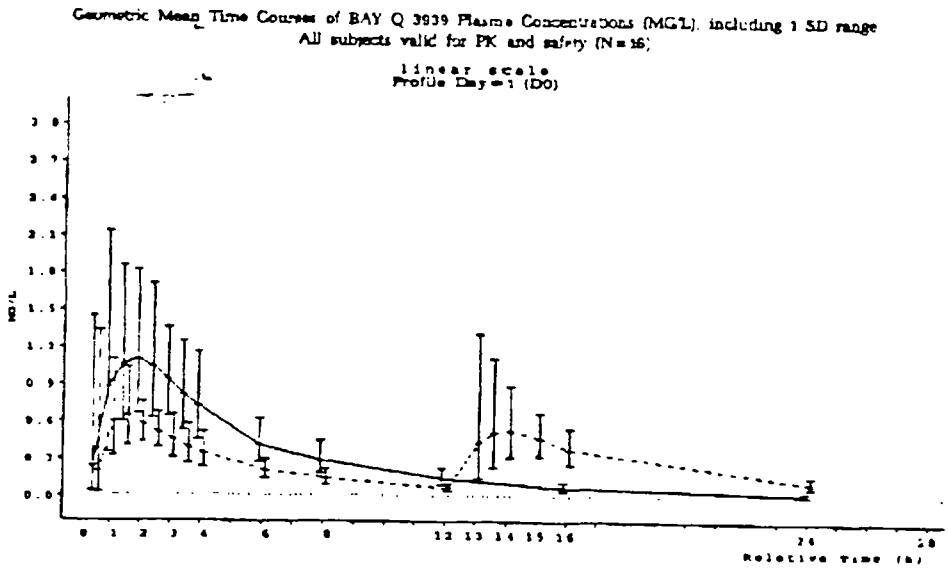
	0-4 Hours	4-8 Hours	8-12 Hours	12-24 Hours	24-28 Hours
Day 1 Ciprofloxacin —	338 ±244	137 ± 75	57 ± 48	27 ± 14	
Day 1 Ciprofloxacin —	161 ± 79	65 ± 38	27 ± 17	123 ± 50	
Day 5 Ciprofloxacin —	368 ± 267	166 ± 90	53 ± 40	30 ± 19	11 ± 8
Day 5 Ciprofloxacin —	196 ± 94	82 ± 51	31 ± 22	128 ± 50	29 ± 12

a IR = Immediate-release ciprofloxacin; collection times for this formulation (given BID) are referenced to the first dose of a 24-hour cycle.
See Study 10325

Do PK parameters change with time following chronic dosing?

The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new — formulation to healthy male subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation.

The peak to trough (PTF) ratios were 4.61 for the CIPRO® XR formulation and was 3.01 for the IR formulation. The presence of an IR component in the CIPRO® XR product may be the cause for higher ratio.



Note. Solid line = 500 mg BAY q 3939 od, dashed line = 250 mg BAY q 3939 bid
Values below LOQ were replaced by half of LOQ in calculations if at least 2/3 of the data were above LOQ.

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

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

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

	Ciprofloxacin 500 mg QD			Ciprofloxacin 250 mg BID		
	N	Mean	Range	N	Mean	Range
Plasma concentration (mg/L)	23	0.13	0-1.6	22	0.20	0-0.6
Urine concentration (mg/L)	24	37	3 6-177.2	21	65	6 6-308 8

What are the basic PK parameters?

The PK parameters in healthy volunteers are given below:

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

	C_{max} (mg/L)	AUC_{0-24h} (mg•h/L)	$T_{1/2}$ (hr)	T_{max} (hr)§
CIPRO — 500 mg QD	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0 – 2.5)
CIPRO 250 mg BID	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5 – 2.5)

§ median (range)

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

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

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

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

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with mild to moderate renal impairment. The package insert for Cipro® immediate release tablets states that a dose adjustment is necessary only for patients with severe renal dysfunction (creatinine clearance = 29 mL/min), and for patients on hemodialysis or peritoneal dialysis. No dose adjustment is proposed for patients with renal impairment. There are several assumptions underlying this proposal:

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

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

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

Based upon what is known about exposure-response relationships and their variability, and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these subgroups?

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

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

c) gender
N/A

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

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

	Ciprofloxacin 500 mg PO QD x 3 days N = 199		Cipro® 250 mg PO BID x 3 days N = 223	
	N/n	%	n/n	%
All Patients	188/199	94.5	209/223	93.7
White	146/154	94.8	166/179	92.7
Black	17/17	100.0	18/18	100.0
Hispanic	18/21	85.7	19/20	95 0
Other	7/7	100 0	6/6	100 0

See Study 100346, Table 14.2/4

e) renal impairment

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

f) hepatic impairment

No significant changes in the pharmacokinetics of ciprofloxacin have been observed in studies of patients with stable chronic cirrhosis of the liver. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. There is no difference in the proposed labeling for CIPRO® XR with respect to hepatic insufficiency from that of immediate- release ciprofloxacin. This proposal is acceptable.

g) what pregnancy and lactation use information is there in the application?

Reproduction studies were performed in rats and mice using oral doses of ciprofloxacin up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 mg/kg and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies any potential risk to the fetus. There were 7 pregnancies in Study 100346 (3 in the CIPRO® XR group and 4 in the Cipro 250 mg). Four of the pregnancies resulted in spontaneous abortions (2 in each group). There is one ongoing pregnancy in each of the two treatment groups as of the date of this summary. One patient in the Cipro 250 mg gave birth to a full-term infant via

normal vaginal delivery during the study period. There were neither maternal complications nor infant abnormalities. The infant's Apgar score at 1 and 5 minutes was 8 and 9, respectively.

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

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

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

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

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

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

Results:

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

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

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

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

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

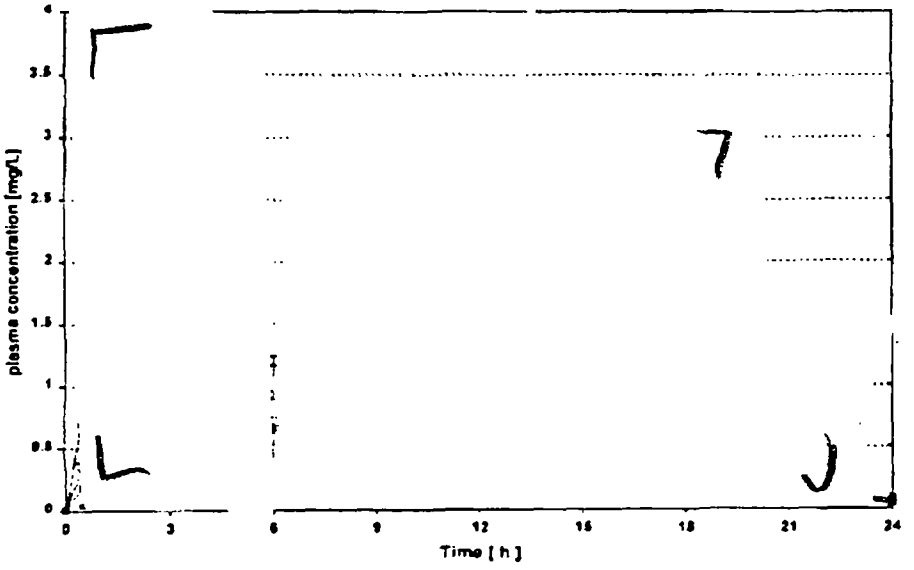
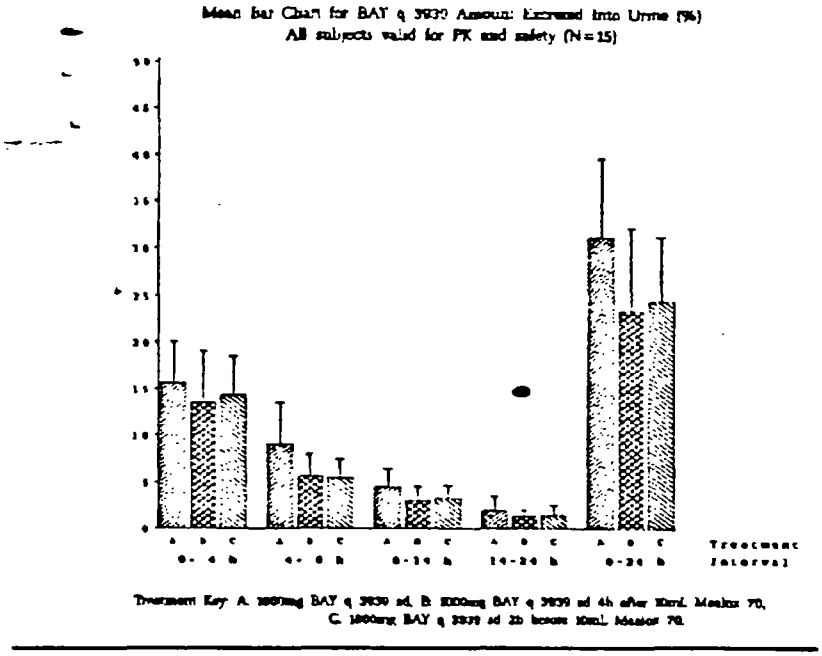


Table 11.5.4-1: Mean ratios and 90% confidence intervals for primary parameters AUC and C_{max} of ciprofloxacin

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

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

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

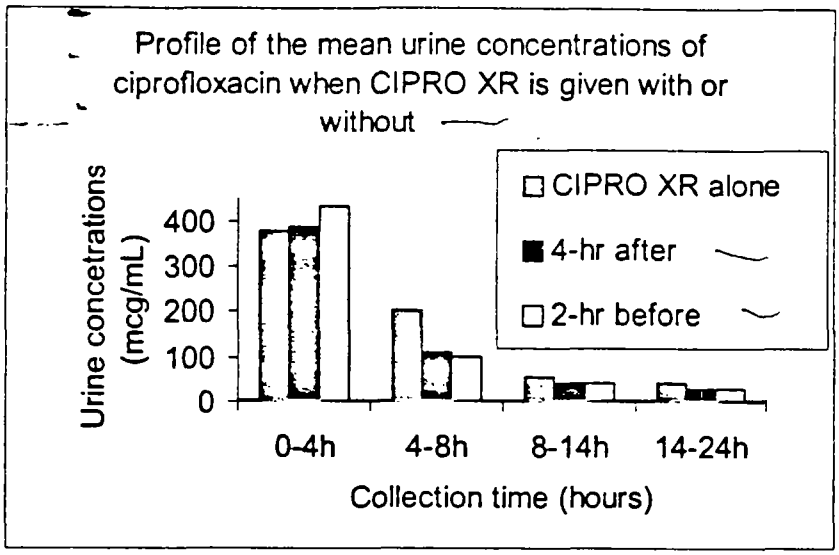


The applicant proposes that the CIPRO® XR label should recommend that CIPRO® XR be administered either 6 hours after, or 2 hours before antacid products. To determine if this is feasible, ciprofloxacin urine concentrations in this study were compared to *in vitro* minimum effective concentrations (MIC_{90})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

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

Collection time (h)	CIPRO® XR alone	4 hr after —— ®	2 hr before —— ®
0-4	(mean = 377)	(mean = 387)	(mean = 434)
4-8	(mean = 203)	(mean = 112)	mean = 103)
8 - 14	(mean = 58)	(mean = 43)	(mean = 46)
14-24	(mean = 44)	(mean = 32)	(mean = 30)

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



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

As shown above, the rate of ciprofloxacin absorption was not affected by —. The extent of systemic absorption (AUC) was reduced by about 26% after co-administration of — given 2 hours before or 4 hours after ciprofloxacin administration. The amount of ciprofloxacin excreted into urine over 0-24 hours was not significantly decreased following pre-treatment with —, and urine concentrations exceeded the MIC_{90} for *E. coli* by at least 100-fold. CIPRO® XR can be administered at least 2 hours before or 6 hours after — is administered.

Omeprazole:

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

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

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

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

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

PK parameters of ciprofloxacin

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

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

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

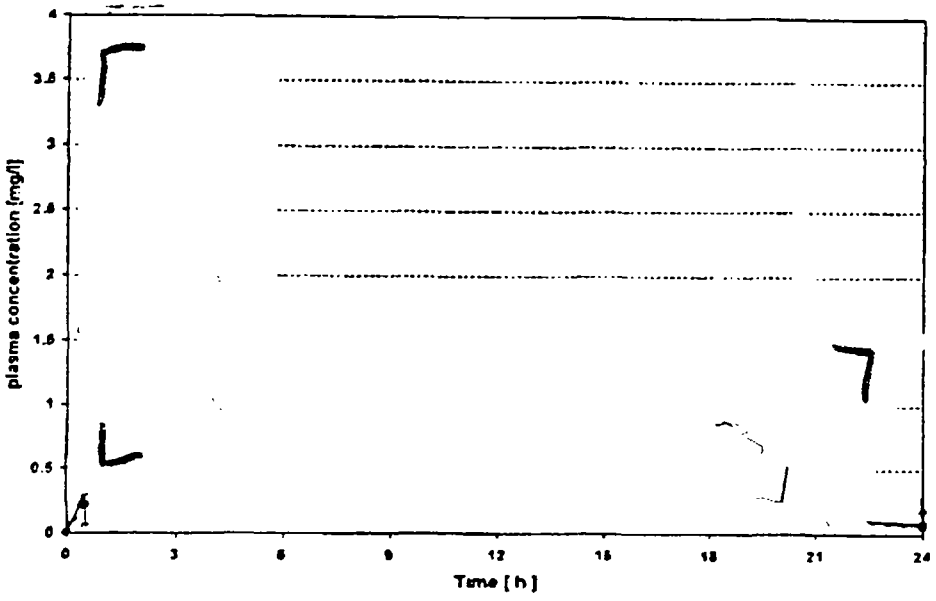


Table 3-1: Pharmacokinetics of ciprofloxacin following administration of 1000 mg alone or with omeprazole (40 mg/day)

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

*median (range)

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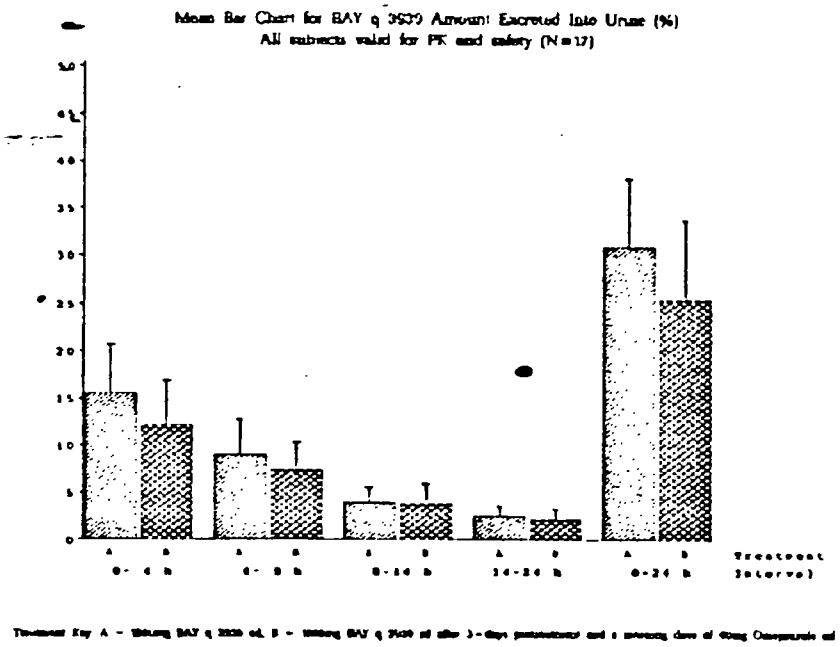

In the urine, slightly decreased ciprofloxacin concentrations were observed for the combination treatments for the interval compared with the mono-treatment.

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

Collection time post-dosing	CIPRO® XR alone	CIPRO® XR + omeprazole
0-4 hours	(mean = 382)	5 (mean = 460)
4-8 hours	(mean = 169)	(mean = 144)
8-14 hours	(mean = 70)	(mean = 68)
14-24 hours	(mean = 47)	(mean = 47)

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

As shown above, omeprazole slightly reduced the rate and extent of ciprofloxacin exposure. The exposure of ciprofloxacin is decreased (20%) by pre-treatment with omeprazole compared with mono-treatment. However, the amount of ciprofloxacin excreted in urine over 24 hours was not significantly different in the two groups. Moreover, ciprofloxacin urine concentrations in the omeprazole-treated group exceeded the MIC for *E. coli* by at least 100-fold throughout the proposed 24-hour dosing interval. It can be concluded that the decrease in ciprofloxacin plasma and urine concentrations observed with co-administration of omeprazole is not clinically significant for the treatment of uncomplicated UTI.

What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

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

PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles

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

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

What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

CIPRO® XR can be administered without regard to meals.

How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Following are the dissolution testing conditions:

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

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

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages

Number of Pages Redacted 20

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(not releasable,

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

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

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

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

This application is X is not ___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)

How does the bioavailability, in terms of C_{max}, AUC, and C_{min} compare between ___ : ciprofloxacin and immediate release ciprofloxacin?

How do urinary concentration of ciprofloxacin obtained with the ___ compare to the immediate release?

What effect does the administration of food, antacids, and omeprazole have on the absorption of ciprofloxacin from the ___ tablet?

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

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

Signature _____ _____

Primary Reviewer **Team Leader/Secondary Reviewer**

cc:

HFD-590: /NDA 21-473
/PM/SalibaJ

HFD-880: /BiopharmTL/DavitB
/Biopharm/MeyerJ

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

/s/

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

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