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**APPROVAL PACKAGE FOR:**

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**21-554**

**Statistical Review(s)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF BIostatISTICS

## Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-554  
Names of drug: Cipro XR  
Applicant: Bayer  
Indication: Complicated Urinary Tract Infection  
Documents reviewed: \\CDSESUB1\N21554\N\_000\2002-10-29\  
Project manager: Jouhayna Saliba  
Clinical reviewer: Joyette Meyer, Pharm.D.  
Dates: Received 10/29/02; user fee (10 months) 08/29/03  
Statistical reviewer: Ruthanna Davi, M.S.  
Statistics team leader: Karen Higgins, Sc.D.  
Biometrics division director: Mohammad Huque, Ph.D.

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## 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

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### 1.1 CONCLUSIONS AND RECOMMENDATIONS

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

### 1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR in the treatment of complicated urinary tract infection. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily (QD) Modified Release Tablets 1000 mg versus Conventional Ciprofloxacin 500 mg Tablets BID in the 7 to 14 Day Treatment of Patients with Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis". This study will be thoroughly reviewed within this document.

### 1.3 PRINCIPAL FINDINGS

For the controlled clinical trial submitted in support of the efficacy of Cipro XR, the by-treatment group comparisons of the primary efficacy endpoint (i.e., bacteriologic outcome at TOC) were not consistent across infection types. A treatment-by-infection-type interaction was observed indicating that the treatment effect is different for AUP patients and cUTI patients and as such these two strata should be considered separately.

*Within the cUTI stratum*, it is the opinion of this reviewer that Cipro XR has been shown to be noninferior to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group. Disproportionately more subjects in the Cipro XR arm were excluded from the PP analysis group for no valid TOC urine culture (which most commonly was due to adverse event or protocol violation). The majority of these subjects were considered failures in the mITT analysis since their bacteriological response at TOC was likely missing or indeterminate. Within the cUTI stratum in the mITT group, the noninferiority criterion was not met.

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

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

- The eradication rates at follow-up for the cUTI subjects were higher in the Cipro XR group than in the Cipro® group. Conversely, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro® group than in the Cipro XR group. These trends are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata.
- The clinical success rates at TOC for the cUTI subjects in the PP analysis group were slightly higher in the Cipro XR group than in the Cipro® group. The clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro® and Cipro XR groups in the PP analysis group. The Cipro XR group had slightly lower clinical success rates than the Cipro® group in the mITT analysis.
- The clinical success rates at the follow-up visit for the cUTI subjects in the PP analysis group were higher in the Cipro XR group than in the Cipro® group. Conversely, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR group than in the Cipro® group in the PP analysis group. Similar trends were observed in the mITT analysis. These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint.

Examination of the primary efficacy endpoint by age, race, and gender indicated that in cUTI subjects, the difference in eradication rates between the two treatment groups was greatest in the age group 65 to 74 years. Also for cUTI subjects, the differences in eradication rates were fairly constant across races. And the difference in eradication rates was larger for males than females in cUTI subjects. The differences in eradication rates in AUP subjects between the two treatment groups were difficult to judge because of the small number of subjects in each subcategory but appeared to be fairly constant across age, race, and gender subcategories.

Tabulations of the bacteriologic success at the TOC visit were fairly numerically consistent across treatment groups for each of the organisms studied.

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## 2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

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### 2.1 INTRODUCTION AND BACKGROUND

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR for the treatment of complicated urinary tract infection and acute uncomplicated pyelonephritis. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily (QD) Modified Release Tablets 1000 mg versus Conventional Ciprofloxacin 500 mg Tablets BID in the 7 to 14 Day Treatment of Patients with Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis". The primary objective of the study was to prove that the bacteriological eradication rate using Cipro XR is not inferior to that of conventional Ciprofloxacin at the test of cure visit in patients with complicated urinary tract infections or acute uncomplicated pyelonephritis.

## 2.2 DATA ANALYZED AND SOURCES

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR for the treatment of complicated urinary tract infection and acute uncomplicated pyelonephritis. The following data sets were submitted electronically and utilized in the review of this study.

\\CDSesub1\N21554\N\_000\2002-10-29\crt\datasets\100275\analysis.xpt  
\\CDSesub1\N21554\N\_000\2002-10-29\crt\datasets\100275\visit.xpt

At the reviewer's request (at the pre-NDA meeting) the sponsor created and submitted the analysis.xpt data set. The analysis.xpt data set was particularly helpful in the investigation of the efficacy results and this reviewer is appreciative of the sponsor's willingness to submit the data in this format. All submitted data sets were found to be clearly documented and well organized.

## 2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

### 2.3.1 REVIEW OF STUDY NUMBER BAY-Q3939-100275

#### 2.3.1.1 Study Design, Protocol, and Protocol Amendments

This was a multicenter, prospective, randomized, double-blind, parallel group, phase III clinical trial conducted at 100 centers in the United States and Canada. The primary objective of this study was to determine if Cipro XR 1000 mg PO QD for seven to fourteen days was non-inferior to conventional ciprofloxacin (Cipro®) 500 mg PO BID for seven to fourteen days in the treatment of patients with complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP).

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

- Men or non-pregnant women, 18 years of age or older;
- For cUTI, patients must have presented with one or more of the following: dysuria, urgency, frequency, suprapubic pain, back pain, flank pain, CVA pain and tenderness, and fever ( $>38^{\circ}\text{C}/100.4^{\circ}\text{F}$  orally) with or without chills;
- For cUTI patients must have at least one or more the following underlying conditions: indwelling urinary catheter, 100 mL of residual urine after voiding, neurogenic bladder, obstructive uropathy due to nephrolithiasis, tumor or fibrosis, and urinary retention in men possibly due to benign prostatic hypertrophy;
- For AUP, patients must have presented with clinical signs and symptoms of an ascending UTI, manifested by all three of the following: fever ( $>38^{\circ}\text{C}/100.4^{\circ}\text{F}$  orally), chills, and flank pain;
- For AUP, patients may also have had any of the following: CVA tenderness, nausea, dysuria, nocturia, frequency, urgency, suprapubic or lower back pain;
- Onset of symptoms  $\leq 72$  hours prior to study entry (original protocol dated 01/11/2001)  
Timing of onset of symptoms not restricted (amendment 4 dated 09/17/2001);

- Women of childbearing potential were required to use two reliable methods of contraception during exposure to study drug; and
- Obtained one pretreatment clean-catch midstream urine sample within 48 hours of enrollment in the study (study enrollment and treatment were permitted prior to the availability of urine culture results).

For purposes of the efficacy analysis subjects must have, a positive culture (defined as  $\geq 10^5$  CFU/mL for a causative pathogen), pyuria (defined as  $\geq 10$  leukocytes/mm<sup>3</sup> in unspun urine specimens or  $>5$  WBC/hpf in spun urine specimens), and a causative pathogen(s) that is susceptible to ciprofloxacin in vitro. For complete listing of exclusion criteria, please see study protocol.

After the inclusion/exclusion criteria were satisfied and written informed consent was obtained, patients were stratified based on the presence or absence of AUP (stratum 1: patients with AUP, stratum 2: patients without AUP but with cUTI) and randomly assigned to receive one of the following two treatments.

- Cipro XR 1000 mg QD for seven to fourteen days or
- Cipro® 500 mg BID for seven to fourteen days

The primary efficacy variable was defined to be the bacteriological response at the test-of-cure visit (TOC). Bacteriological response at the TOC visit was graded as eradication, persistence, superinfection, new infection, or indeterminate. The following definitions are from the sponsor's study report.

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

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

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

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

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

Bacteriological response at the follow-up visit and clinical responses at the test-of-cure and follow-up visits were considered secondary variables. Bacteriological response at the follow-up visit was graded as continued eradication, persistence, superinfection, recurrence, new infection, or indeterminate. The following definitions are from the sponsor's study report.

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

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

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

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

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

**Indeterminate:** Bacteriological outcome could not be evaluated for any reason (eg, posttreatment culture was not obtainable). The reason for an indeterminate evaluation must have been documented.

Clinical outcome at the TOC visit was graded as clinical cure, clinical failure, or indeterminate. The following definitions are from the sponsor's study report.

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

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

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

Clinical outcome at the late follow-up visit was graded as continued clinical cure, failure, relapse, or indeterminate.

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

**Failure:** An outcome of failure was carried forward from the TOC visit.

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

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

As indicated above in the definitions of the endpoints, the protocol specified that subjects with an indeterminate evaluation at the TOC time point should be excluded from the efficacy analysis for that endpoint. The protocol did not specify how indeterminate responses at the follow-up visit would be handled for either the bacteriologic or clinical endpoints, however; in the study report, indeterminate responses at the follow-up visit were excluded from the analysis. By definition, the per-protocol analysis group excluded subjects, for whom the primary endpoint is not observed, in essence implementing the protocol-defined exclusion of subjects with indeterminate responses for the bacteriologic outcome at TOC. [Please see "Figure 1: Patient Disposition and Analysis Groups" for the frequency of exclusion due to "no TOC urine culture".] However, for the other endpoints (i.e., bacteriologic outcome at follow-up and clinical outcome at TOC and follow-up) the division commonly uses the established per-protocol analysis group and considers indeterminate responses for these endpoints failures. The analyses in this review will be conducted in accordance with this custom.

As per the 1998 draft FDA guidance, "Uncomplicated Urinary Tract Infection – Developing Antimicrobial Drugs for Treatment", the original protocol defined the timing of the test-of-cure visit to be within 5 and 9 days post-treatment and the timing of the follow-up visit to be within 28 and 42 days post-treatment. However, on August 30, 2002 (approximately 1.5 months after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 5 to 11 days post-treatment. The follow-up visit window was not modified. Under the newly amended time frame for the TOC visit, 17 subjects who previously were ineligible for the efficacy analysis at the TOC visit were now considered eligible for analysis. The study report does not indicate that this protocol amendment was made prior to data analysis and in fact states that the amendment was made since a number of patient visits occurred outside the protocol-specified TOC window, possibly indicating that examination of the efficacy data had begun. Further exploration of this issue is given in section 2.3.1.2.

The primary efficacy objective of the study was to demonstrate non-inferiority of Cipro XR to Cipro® in terms of the bacteriological eradication rates at the TOC visit in patients with cUTI or AUP. A two-sided 95% confidence interval for the weighted difference between treatment groups was to be constructed, using Mantel-Haenszel weights (weighting by infection type). The difference was to be calculated as the proportion of subjects in the Cipro XR treatment group with eradication at the test-of-cure visit minus the same such proportion in the Cipro® group. Non-inferiority was defined as the lower limit of the two-sided 95% confidence interval for the difference between treatment groups being greater than -10%. Analysis of infection type by treatment interaction for the primary efficacy variable was planned using either the Breslow-Day test or Zelen's test.

The protocol-specified group that was to be used in the primary efficacy analysis was the per-protocol (PP) group defined as subjects meeting all of the following criteria.

- All inclusion/exclusion criteria were met;
- Study drug was given for a minimum of three days if the treatment result was failure, or a minimum of seven days if the treatment result was success;
- Bacteriological outcomes were determined at the TOC visit unless the patient's outcome was early treatment failure (patients with a response of Indeterminate at the TOC visit were invalid for the efficacy evaluation);
- No other systemic antibacterial agent was administered with the study drug during the study period up through the TOC visit unless the patient failed treatment;
- Adequate compliance must have been documented for each patient, with  $\geq 80\%$  of study medication taken;
- No protocol violation occurred during the course of therapy influencing treatment efficacy; and
- Study blind was not broken.

A modified intent-to-treat (mITT) analysis including all patients who received at least one dose of study drug and had a baseline pathogen was not protocol-specified but will be conducted by this reviewer. Patients with missing or indeterminate efficacy evaluations will be included and counted as nonsuccesses in all efficacy analyses carried out in the mITT population. While the PP efficacy results were designated in the protocol as the primary interest, it is division policy to consider the results of the mITT group of at least as much importance as that of the PP group for non-inferiority trials. Therefore this review will include discussion of the results from both analysis groups.

The protocol originally specified that 408 patients would be enrolled into the study. This sample size was calculated using the methods of Rodary<sup>1</sup>, based on the previously described primary analysis methods using 90% power and the following assumptions.

- The true eradication rate for each treatment group is 83%,
- The smallest clinically meaningful difference between treatments (delta) is 15%, and
- The subject validity rate is 75%.

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<sup>1</sup> Rodary C, Com-Nougue C, Toumade MF. How to establish equivalence between treatments: a one-sided clinical trial in pediatric oncology. *Stat Med.* 1989;8:593-8.

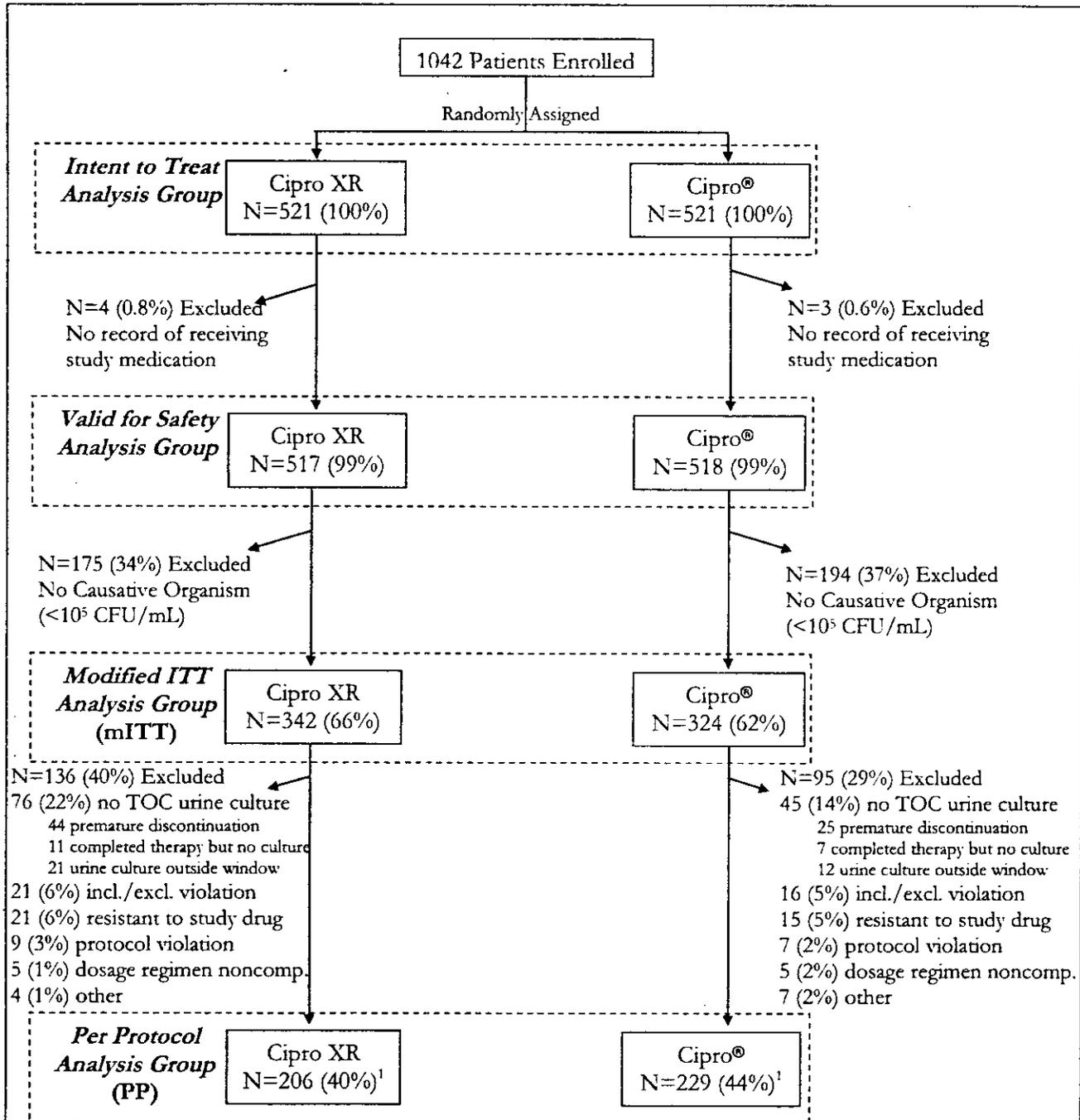
During the study, it became clear that the validity rate would be much lower than 75% because the rate of pretreatment urine culture results with  $\geq 10^5$  CFU/mL of a causative organism was lower than originally anticipated. In addition, the observed eradication rate (88%) was higher than originally predicted (83%) and delta was adjusted from 15% to 10%. The protocol was amended three times to address these issues. First, approximately thirteen months after the finalization of the protocol the sample size was revised to reflect a delta of 10% (rather than 15%). This resulted in the need for 886 patients to be enrolled in order to obtain 664 valid patients. Approximately nine months later, the sample size calculation was revised again, this time to reflect an increase in the observed eradication rate (from 83% to 85%), decrease in power (from 90% to 85%), and decrease in the validity rate (from 75% to 50%). This resulted in the need for 948 patients to be enrolled in order to obtain the now necessary 474 valid patients. The third modification in the sample size calculation occurred approximately nine months later. This revision reflected an increase in the observed eradication rate (from 85% to 88%) and a decrease in the validity rate (from 50% to 39%). The result was that 1036 patients were needed to be enrolled to obtain the now necessary 404 valid patients. All of these sample size modifications were made prior to the study being unblinded and before any efficacy analyses were completed. Therefore it is the opinion of this reviewer that these sample size revisions in no way compromised the integrity of this study and no adjustment in the significance level ( $\alpha$ ) is warranted.

#### 2.3.1.2 Results

The pivotal study enrolled 1042 patients at 100 centers. Five hundred twenty one were randomly assigned to treatment with Cipro XR and 521 were randomly assigned to treatment with Cipro®. Patient inclusion in and exclusion from the *intent-to-treat, valid for safety, modified intent-to-treat (mITT)*, and *per-protocol (PP)* analysis data sets are described in Figure 1.

As indicated in Figure 1, seven subjects were excluded from the valid for safety analysis group, as there was no record of them receiving study medication. The only reason for further exclusions from the mITT analysis group in both treatments groups was no causative organism reported in a quantity  $\geq 10^5$  CFU/mL. The Cipro® group had a slightly higher rate of patients (37%) with no causative organisms at a level  $\geq 10^5$  CFU/mL compared with the Cipro XR group (34%). Further exclusions from the PP analysis group were made for the following reasons; no TOC urine culture, violation of inclusion and/or exclusion criteria, organism resistant to study drug, protocol violation, noncompliance with the dosage regimen, and other (including inadequate duration of treatment, posttherapy antibiotics, and concomitant antimicrobial therapy). The Cipro XR group had a statistically significantly ( $p=0.005$ ) higher rate (22%) of patients who had no valid TOC urine culture result compared to the Cipro® group (14%). This disproportionate exclusion is primarily due to subjects' premature discontinuation from the study and is of concern particularly since more patients in the experimental treatment group were affected. The most common reasons for premature discontinuation were protocol violation and adverse event. This may be an indication that some aspect of the effect of Cipro XR is causing patients to drop out. The rates of the other exclusions were similar between the two treatment groups.

Figure 1: Patient Disposition and Analysis Groups



1. Of these 206 Cipro XR subjects, 166 had cUTI and 40 had AUP. Of these 229 Cipro® subjects, 177 had cUTI and 52 had AUP.

Demographic and baseline variables (including causative organisms) for the PP and valid for safety analysis groups are summarized in Table 1. The weight, body mass index, and health status prior to study entry of Cipro XR subjects were statistically significantly different from those of the Cipro® subjects in the valid for safety analysis group. The means of weight and body-mass-index in the Cipro XR group were slightly lower than those measures in the Cipro® group. More Cipro XR subjects were given a health status rating of "excellent" than were Cipro® subjects. As would be expected since the PP analysis group is a subset of the valid for safety analysis group, trends in the PP analysis group were similar to the results in the valid for safety analysis group. However, these relationships were not statistically significant in the PP analysis group. Note that these endpoints (weight, body mass index, and health status) are likely correlated. These by-treatment imbalances may impact the efficacy and/or safety outcomes and should be kept in mind in interpreting the efficacy and safety results. Other than these variables, the distributions of the demographic and baseline variables were not statistically significantly different across treatment groups.

Examination of demographic and baseline variables by stratum revealed patterns similar to those described above, within each infection type (AUP and cUTI).

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**Table 1: Demographic and Baseline Variables Summary Statistics**

		PP Analysis Group			Safety Analysis Group		
		Cipro XR N=206 <sup>1</sup>	Cipro® N=229 <sup>1</sup>	By-trt. p-value <sup>2</sup>	Cipro XR N=517 <sup>1</sup>	Cipro® N=518 <sup>1</sup>	By-trt. p-value <sup>2</sup>
Age (years)	Mean (Median)	60.1 (66.0)	61.2 (66.0)	0.550	58.9 (63.0)	59.9 (65.0)	0.430
	Range	18.0 – 96.0	18.0 – 92.0		18.0 – 97.0	18.0 – 94.0	
Weight (kg)	Mean (Median)	75.8 (73.6)	78.3 (75.0)	0.213	75.1 (73.2)	77.6 (74.5)	0.041
	Range	43.6 – 129.1	50.0 – 156.8		39.1 – 150.0	44.5 – 174.3	
Body Mass Index	Mean (Median)	26.6 (26.0)	27.4 (26.0)	0.121	26.4 (26.0)	27.4 (26.0)	0.004
	Range	15.6 – 46.8	15.6 – 46.8		15.6 – 46.8	15.6 – 57.2	
Duration of Infection (days)	Mean (Median)	4.7 (3.0)	4.4 (3.0)	0.621	4.7 (3.0)	4.5 (3.0)	0.579
	Range	1.0 – 121.0	1.0 – 34.0		1.0 – 121.0	1.0 – 51.0	
Gender	Female	88 (43%)	102 (45%)	0.736	219 (42%)	219 (42%)	0.979
	Male	118 (57%)	127 (55%)		298 (58%)	299 (58%)	
Race	Caucasian	168 (82%)	177 (77%)	0.736	410 (79%)	414 (80%)	0.783
	Black	19 (9%)	27 (12%)		55 (11%)	48 (9%)	
	Asian	1 (<1%)	1 (<1%)		3 (<1%)	3 (<1%)	
	American Indian	0 (0%)	0 (0%)		1 (<1%)	0 (0%)	
	Hispanic	18 (9%)	24 (10%)		48 (9%)	53 (10%)	
Health Status Prior to Study Entry	Excellent	61 (30%)	43 (19%)	0.069	138 (27%)	100 (19%)	0.037
	Good	106 (51%)	135 (59%)		266 (51%)	302 (58%)	
	Fair	37 (18%)	49 (21%)		108 (21%)	110 (21%)	
	Poor	2 (<1%)	2 (<1%)		5 (<1%)	6 (1%)	
Infection Type	AUP	40 (19%)	52 (23%)	0.401	109 (21%)	111 (21%)	0.892
	cUTI	166 (81%)	177 (77%)		408 (79%)	407 (79%)	
Number of Underlying Conditions for cUTI	AUP	40 (19%)	52 (23%)	0.441	109 (21%)	111 (21%)	0.356
	Zero	0 (0%)	0 (0%)		8 (2%)	8 (2%)	
	One	119 (58%)	140 (61%)		283 (55%)	306 (59%)	
	Two	41 (20%)	33 (14%)		105 (20%)	86 (17%)	
	Three or more	6 (3%)	4 (2%)		12 (2%)	7 (1%)	
Pre-therapy Causative Organisms (subject may have ≥ 1 organism)	Acinetobacter Sp.	0	0	NA	0	1	NA
	Alcaligenes xylosoxidans	0	0		0	1	
	Burkholderia cepacia	1	0		3	0	
	Citrobacter braakii	0	0		0	1	
	Citrobacter freundii	4	4		4	5	
	Citrobacter koseri	1	3		1	3	
	Citrobacter youngae	1	0		1	0	
	Enterobacter aerogenes	4	6		4	6	
	Enterobacter cloacae	2	3		4	5	
	Enterococcus faecalis	19	27		35	40	
	Enterococcus faecium	2	0		3	2	
	Escherichia coli	130	133		206	177	
	Klebsiella oxytoca	1	7		3	9	
	Klebsiella pneumoniae	25	25		40	36	
	Morganella morganii	0	2		0	2	
	Proteus mirabilis	12	14		16	17	
	Providencia rettgeri	0	2		0	3	
	Providencia stuartii	0	0		1	0	
	Pseudomonas aeruginosa	4	3		9	6	
	Serratia liquefaciens	0	0		0	1	
Serratia marcescens	2	4	2	5			
Staphylococcus aureus	6	4	8	8			
Staphylococcus saprophyticus	2	2	4	2			
Weeksella virosa	0	1	0	1			

1. Small amount of missing data (≤1%) for various endpoints was ignored.  
2. P-values for categorical variables obtained using a chi-square test. P-values for continuous variables obtained using 1-way ANOVA.

Bacteriological response at the test-of-cure visit is the primary efficacy variable. The results for this endpoint in the overall group and in each of the strata (AUP and cUTI) are summarized in Table 2 for both the PP and mITT analysis groups.

<b>Table 2</b>				
<b>Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)</b>				
	PP Analysis Group		mITT Analysis Group	
	Cipro XR	Cipro®	Cipro XR	Cipro®
<b>All Patients</b>	<b>N=206</b>	<b>N=229</b>	<b>N=342</b>	<b>N=324</b>
<b>Eradication</b>	183 (88.8%)	195 (85.2%)	207 (60.5%)	214 (66.0%)
<b>95% C. I. for Diff. in Prop. (weighted by infection type)</b>	(-2.4%, 10.3%)* <sup>§</sup>		(-12.6%, 2.1%) <sup>§</sup>	
<b>AUP Patients</b>	<b>N=40</b>	<b>N=52</b>	<b>N=71</b>	<b>N=76</b>
<b>Eradication</b>	35 (87.5%)	51 (98.1%)	47 (66.2%)	58 (76.3%)
<b>97.5% C. I. for Diff. in Prop.</b>	(-34.8%, 6.2%) <sup>‡</sup>		(-26.8%, 6.5%) <sup>‡</sup>	
<b>cUTI Patients</b>	<b>N=166</b>	<b>N=177</b>	<b>N=271</b>	<b>N=248</b>
<b>Eradication</b>	148 (89.2%)	144 (81.4%)	160 (59.0%)	156 (62.9%)
<b>97.5% C. I. for Diff. in Prop.</b>	(-0.7%, 16.3%) <sup>‡</sup>		(-13.5%, 5.7%) <sup>‡</sup>	
<b>Breslow-Day test for treatment-by-infection-type interaction in PP group, p-value=0.008</b>				

\*Sponsor's primary efficacy analysis.

<sup>§</sup>Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by infection type).

<sup>‡</sup>Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

The 95% confidence interval for the by-treatment difference in the proportions of subjects with eradication at the TOC visit (Cipro XR - Cipro®) in the PP analysis group excludes the protocol specified noninferiority margin of -10%. Under usual circumstances this along with similar results in the mITT analysis group, would lead to the conclusion that for this endpoint, Cipro XR is noninferior to Cipro®. However, in this case there is a statistically significant treatment-by-infection-type interaction (Breslow-Day test for interaction p-value = 0.008) indicating that the results of the treatment group comparisons between infection types were not consistent. In the PP analysis group, the eradication rates for the AUP subjects were higher in the Cipro® group (98.1%) than in the Cipro XR group (87.5%). Conversely, the eradication rates for the cUTI subjects were higher in the Cipro XR group (89.2%) than in the Cipro® group (81.4%). Such an interaction invalidates the results of the overall group, as the two strata should not be combined since the treatment effect is different for each stratum.

The sponsor suggests that the significance of the treatment-by-infection-type interaction is due to the fact that coincidentally three AUP patients in the Cipro XR group developed new infections while no AUP patients in the Cipro® group developed new infections. Given the sample size in the AUP stratum in each treatment group, the probability of three or more new infections occurring in the Cipro XR group and no new infections occurring in the Cipro® group by chance alone is less than 12%. For completeness, excerpts from the sponsor's study report describing the three cases of new infection are given below.

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

The second patient (82039) is a 19-year-old female with no significant medical history. Concomitant medications included acetaminophen and an oral contraceptive agent. The patient presented with 3 days of signs and symptoms of pyelonephritis, a temperature of 38.5°C (orally), and a WBC count of  $11.6 \times 10^9/L$ . Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro® XR 1000 mg QD, which she received for 8 days. At the TOC visit, the patient's response was evaluated as clinical cure (no remaining signs or symptoms of infection). The WBC count had decreased to  $6.4 \times 10^9/L$ . A repeat urine culture result obtained at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* and *E. faecium* both were identified in a quantity of  $\geq 10^5$  CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient's response was assessed as a continued clinical cure. Urine culture results at follow-up revealed continued eradication of *E. coli* and absence of both *Enterococcus* species.

The third patient (148023) is an 18-year-old female with no significant medical history, and she was not receiving any concomitant medications. The patient presented with 2 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mild/moderate signs and symptoms, a temperature of 38.8°C (orally), and a WBC count of  $9.7 \times 10^9/L$ . Her pretherapy urine culture result was positive for *S. saprophyticus*, and she was assigned randomly to treatment with Cipro® XR 100 mg QD, which she received for 11 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to  $5.5 \times 10^9/L$ . A repeat urine culture result at the TOC visit was negative for *S. saprophyticus* (eradication); however, *E. faecalis* was identified in a quantity of  $\geq 10^5$  CFU/mL (new infection). Alternative antibiotic therapy was prescribed (ciprofloxacin 500 mg BID for 7 days) 18 days following the completion of study drug therapy. At the post-alternative therapy visit the patient's clinical response was evaluated as clinical cure; there was no follow-up bacteriological evaluation.

Although perhaps implied by the clinical explanations given above, ultimately, the sponsor does not suggest that this data be reanalyzed while treating the three AUP patients in the Cipro XR group who developed new infections as successes. The explicit conclusion that the sponsor makes regarding the treatment-by-infection-type interaction is the following.

"The results of the treatment group comparisons between infection types were not consistent... The p-value from the Breslow-Day test for treatment-by-infection-type interaction was 0.008, indicating that the treatment effect was different between pyelonephritis patients and complicated UTI patients."

This reviewer is in agreement with this conclusion.

The Division has considered post-hoc analyses aimed at eliminating the significance of the treatment-by-infection-type interaction. In particular an analysis considering the three patients described above as successes was conducted. Although this reassignment of

response did eliminate the significance of the interaction, in the opinion of this reviewer these types of analyses are not appropriate. The following description is given as statistical justification for why post-hoc reclassification of response is not appropriate.

Many post-hoc reclassifications schemes where a certain number of failures are considered successes could lead to a p-value for the treatment-by-infection-type interaction that is larger than  $\alpha=0.10$  (i.e., not statistically significant). There are five AUP subjects treated with Cipro XR who did not fall into the "eradication" category. And so as defined in the protocol were not considered successes. Reclassifying three, four, or five of these five failures, as successes would eliminate the significance of the interaction. There are several ways you can group the five failures into groups of size three. For simplicity suppose the subject numbers for the 5 failures are 1, 2, 3, 4, and 5. Then possible groups of size 3 are:

- |         |         |         |         |
|---------|---------|---------|---------|
| 1, 2, 3 | 1, 3, 4 | 2, 3, 4 | 3, 4, 5 |
| 1, 2, 4 | 1, 3, 5 | 2, 3, 5 |         |
| 1, 2, 5 | 1, 4, 5 | 2, 4, 5 |         |

Mathematically this is described as "five choose three" and is written  $\binom{5}{3} = 10$ , meaning

that there are 10 ways to choose three of five patients. The number of ways you can group the 5 failures into groups of size 4:

- |            |            |
|------------|------------|
| 1, 2, 3, 4 | 1, 3, 4, 5 |
| 1, 2, 3, 5 | 2, 3, 4, 5 |
| 1, 2, 4, 5 |            |

In other words,  $\binom{5}{4} = 5$ , meaning that there are 5 ways to choose four of five patients.

Finally, there is one way to group the five failures into a group of 5. So in total there are 16 regroupings involving the AUP subjects treated with Cipro XR who were failures in the original analysis that would eliminate the significance of the treatment-by-infection-type interaction.

In addition, there are 33 cUTI subjects treated with Cipro® who did not fall into the "eradication" category and as per-protocol were not considered successes. Reclassifying 17 to 32 of these 33 failures as successes would eliminate the significance of the interaction. The number of ways you can regroup the 33 failures to remove the significance of the interaction test follows:

$\binom{33}{17} = 1166803110$	$\binom{33}{21} = 354817320$	$\binom{33}{25} = 13884156$	$\binom{33}{29} = 40920$
$\binom{33}{18} = 1037158320$	$\binom{33}{22} = 193536720$	$\binom{33}{26} = 4272048$	$\binom{33}{30} = 5456$
$\binom{33}{19} = 818809200$	$\binom{33}{23} = 92561040$	$\binom{33}{27} = 1107568$	$\binom{33}{31} = 528$
$\binom{33}{20} = 573166440$	$\binom{33}{24} = 38567100$	$\binom{33}{28} = 237336$	$\binom{33}{32} = 33$

So in total there are more than 4 billion regroupings involving the cUTI subjects treated with Cipro® who were failures in the original analysis that would eliminate the significance of the treatment-by-infection-type interaction.

The large number of possible reclassifications leading to an insignificant treatment-by-infection-type interaction illustrates the difficulties associated with post-hoc reassignment of response. As such, it is not surprising that out of more than 4 billion possible groupings, at least one can be portrayed as having clinically sound justification. From a statistical perspective, post-hoc reassignment of response and re-analyses are not appropriate. And conclusions should be drawn from the analysis of the subjects' responses as they were observed. The p-value from the Breslow-Day test for treatment-by-infection-type interaction using the observed data was 0.008, indicating that there is 0.8% chance of obtaining these results or something more extreme if no treatment-by-infection-type interaction exists. This is overwhelming statistical evidence that a treatment-by-infection-type interaction does exist. Such an interaction invalidates the results of the overall group, as the two strata should not be combined since the treatment effect is different for each stratum.

Since the random assignment of treatment was stratified by infection type, it is appropriate to consider the results of each stratum alone with an adjustment for multiple comparisons. Since no multiple comparison procedure was pre-specified, a Bonferroni correction has been implemented. Within the AUP stratum, the protocol-specified noninferiority criterion (exclusion of -10%) has not been met. In fact within the AUP stratum, Cipro XR appears to be worse than Cipro® for the eradication at TOC endpoint in the PP analysis group (as evidenced by the confidence interval for the by-treatment group difference being primarily below zero). Within the cUTI stratum, the protocol-specified noninferiority criterion (exclusion of -10%) is achieved. In fact within the cUTI stratum, Cipro XR is nearly statistically significantly better than Cipro® for the eradication at TOC endpoint in the PP analysis group (as evidenced by the confidence interval for the by-treatment group difference being nearly completely above zero). It is the opinion of this reviewer that Cipro XR has been shown to be noninferior to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group *within the cUTI stratum*. Noninferiority of Cipro XR to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group *in the AUP stratum* has not been demonstrated.

The mITT analysis group includes all subjects who had a baseline causative organism and received at least one dose of study medication. Thus this mITT analysis group includes the 136 (40%) Cipro XR subjects and 95 (29%) Cipro® subjects who were excluded from the PP analysis group (see Figure 1). Note that there were disproportionately and statistically significantly ( $p=0.004$ ) more of these subjects in the Cipro XR group than in the Cipro® group (40% versus 29%). Subjects who are included in the mITT group but for whom the bacteriological response at TOC was missing or indeterminate were considered failures in this analysis. Similar patterns to that of the PP analysis group, were observed in the mITT analysis group for the AUP subjects (see Table 2). However, for the cUTI subjects, the pattern was different from the PP analysis group in that the eradication rate at TOC for

Cipro XR no longer appeared to be better than that of Cipro®. This may be a suggestion that the nearly statistically significantly superior result observed in the PP analysis group was an artifact of the disproportionate exclusion of more Cipro XR subjects than Cipro® subjects. In summary, for the mITT analysis, it is the opinion of this reviewer that the noninferiority of Cipro XR to Cipro® in terms of the bacteriological TOC endpoint has not been demonstrated within the AUP stratum. Within the cUTI group in the mITT analysis group, the noninferiority criterion is not met, as the lower bound of the 97.5% confidence interval for the by-treatment difference in proportions is -13.5%. The results do not indicate that Cipro XR is nearly statistically significant superior to Cipro® as was observed in the PP analysis group.

Bacteriological response at the follow-up was a secondary efficacy variable. The results for this endpoint in the overall group and in each of the strata (AUP and cUTI) are summarized in Tables 3a for both the PP and mITT analysis groups.

<b>Bacteriologic Success at the Follow-up Time Point (Secondary Efficacy Endpoint)<sup>†</sup></b>				
	PP Analysis Group		mITT Analysis Group	
	Cipro XR	Cipro®	Cipro XR	Cipro®
<b>All Patients</b>	<b>N=206</b>	<b>N=229</b>	<b>N=342</b>	<b>N=324</b>
Continued Eradication	124 (60.2%)	115 (50.2%)	146 (42.7%)	130 (40.1%)
95% C. I. For Diff. In Prop. (weighted by infection type)	(1.1%, 19.7%) <sup>§</sup>		(-4.5%, 10.4%) <sup>§</sup>	
<b>AUP Patients</b>	<b>N=40</b>	<b>N=52</b>	<b>N=71</b>	<b>N=76</b>
Continued Eradication	25 (62.5%)	35 (67.3%)	35 (49.3%)	41 (53.9%)
97.5% C. I. For Diff. In Prop.	(-27.3%, 17.7%) <sup>‡</sup>		(-23.1%, 13.8%) <sup>‡</sup>	
<b>cUTI Patients</b>	<b>N=166</b>	<b>N=177</b>	<b>N=271</b>	<b>N=248</b>
Continued Eradication	99 (59.6%)	80 (45.2%)	111 (41.0%)	89 (35.9%)
97.5% C. I. For Diff. In Prop.	(2.5%, 26.4%) <sup>‡</sup>		(-4.5%, 14.6%) <sup>‡</sup>	
<b>Breslow-Day test for treatment-by-infection-type interaction in PP group, p-value=0.1047</b>				

<sup>§</sup>Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by infection type).

<sup>‡</sup>Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation.

<sup>†</sup>Indeterminate responses were included and considered failures in this efficacy analysis.

In the PP analysis group, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro® group (67.3%) than in the Cipro XR group (62.5%). Conversely, the eradication rates for the cUTI subjects were higher in the Cipro XR group (59.6%) than in the Cipro® group (45.2%). Similar trends were observed in the mITT analysis group.

The trends in the bacteriologic endpoint at the follow-up visit are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata. The Breslow-Day test for interaction indicates that for the follow-up visit, there is a nearly statistically significant ( $\alpha=0.01$ ) treatment-by-infection-type interaction ( $p=0.1047$ ). The replication of the same type of treatment-by-infection type interaction in

the bacteriologic endpoint at this time point is due in part to the fact that bacteriologic failures at the TOC visit were carried forward to the follow-up visit.

Clinical response at the TOC and follow-up visit were secondary efficacy variables. The results for these endpoints in the overall group and in each of the strata (AUP and cUTI) are summarized in Tables 3b for both the PP and mITT analysis groups.

<b>Table 3b</b>				
<b>Clinical Success at the Test-of-Cure Time Point (Secondary Efficacy Endpoint)<sup>†</sup></b>				
	PP Analysis Group		mITT Analysis Group	
	Cipro XR	Cipro®	Cipro XR	Cipro®
<b>All Patients</b>	<b>N=206</b>	<b>N=229</b>	<b>N=342</b>	<b>N=324</b>
<b>Clinical Cure</b>	198 (96.1%)	211 (92.1%)	234 (68.4%)	240 (74.1%)
<b>95% C. I. for Diff. in Prop. (weighted by infection type)</b>	(-0.3%, 8.5%) <sup>§</sup>		(-12.5%, 13.0%) <sup>§</sup>	
<b>AUP Patients</b>	<b>N=40</b>	<b>N=52</b>	<b>N=71</b>	<b>N=76</b>
<b>Clinical Cure</b>	39 (97.5%)	50 (96.2%)	50 (70.4%)	58 (76.3%)
<b>97.5% C. I. for Diff. in Prop.</b>	(-15.3%, 21.1%) <sup>‡</sup>		(-22.0%, 10.4%) <sup>‡</sup>	
<b>cUTI Patients</b>	<b>N=166</b>	<b>N=177</b>	<b>N=271</b>	<b>N=248</b>
<b>Clinical Cure</b>	159 (95.8%)	161 (91.0%)	184 (67.9%)	182 (73.4%)
<b>97.5% C. I. for Diff. in Prop.</b>	(-1.1%, 10.8%) <sup>‡</sup>		(-14.4%, 3.5%) <sup>‡</sup>	
<b>Clinical Success at the Follow-up Time Point (Secondary Efficacy Endpoint)*</b>				
	PP Analysis Group		mITT Analysis Group	
	Cipro XR	Cipro®	Cipro XR	Cipro®
<b>All Patients</b>	<b>N=206</b>	<b>N=229</b>	<b>N=342</b>	<b>N=324</b>
<b>Continued Clinical Cure</b>	150 (72.8%)	151 (65.9%)	179 (52.3%)	173 (53.4%)
<b>95% C. I. for Diff. in Prop. (weighted by infection type)</b>	(-1.4%, 15.9%) <sup>§</sup>		(-8.3%, 6.8%) <sup>§</sup>	
<b>AUP Patients</b>	<b>N=40</b>	<b>N=52</b>	<b>N=71</b>	<b>N=76</b>
<b>Continued Clinical Cure</b>	30 (75.0%)	42 (80.8%)	40 (56.3%)	50 (65.8%)
<b>97.5% C. I. for Diff. in Prop.</b>	(-25.4%, 13.9%) <sup>‡</sup>		(-27.4%, 8.5%) <sup>‡</sup>	
<b>cUTI Patients</b>	<b>N=166</b>	<b>N=177</b>	<b>N=271</b>	<b>N=248</b>
<b>Continued Clinical Cure</b>	120 (72.3%)	109 (61.6%)	139 (51.3%)	123 (49.6%)
<b>97.5% C. I. for Diff. in Prop.</b>	(-0.6%, 22.0%) <sup>‡</sup>		(-8.2%, 11.5%) <sup>‡</sup>	

<sup>§</sup>Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by infection type).

<sup>‡</sup>Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

<sup>†</sup>Indeterminate responses were included and considered failures in this efficacy analysis.

In the PP analysis group, the clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro® and Cipro XR groups (97.5% and 96.2%, respectively). The clinical success rates for the cUTI subjects were slightly higher in the Cipro XR group (95.8%) than in the Cipro® group (91.0%).

In the PP analysis group, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR (75.0%) group than in the Cipro® group (80.8%). Conversely, the clinical success rates for the cUTI subjects were slightly higher in the Cipro XR group (72.3%) than in the Cipro® group (61.6%). These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint. The p-value for the Breslow-Day test for interaction for the clinical endpoint at follow-up is 0.1367.

The original protocol defined the timing of the test-of-cure visit to be within 5 and 9 days post-treatment and the timing of the follow-up visit to be within 28 and 42 days post-treatment. However, on August 30, 2002 (approximately 1.5 months after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 5 to 11 days post-treatment. The follow-up visit window was not modified. Under the newly amended time frame for the TOC visit, 17 subjects who previously were ineligible for the efficacy analysis at the TOC visit were now considered eligible for analysis. The study report does not indicate that this protocol amendment was made prior to data analysis and in fact states that the amendment was made since a number of patient visits occurred outside the protocol-specified TOC window, possibly indicating that examination of the efficacy data had begun. This reviewer conducted the analyses of the primary endpoint in adherence with the original protocol, i.e., including only the subjects with a test-of-cure visit within the protocol-defined test-of-cure window. The qualitative conclusions from this analysis are not different from those made above (see Table 2) where the amended TOC time frame is used. This provides reassurance that the results of the above analysis likely were not an artifact of the newly defined time frames. The results of the original protocol-defined analysis are summarized in Table 4.

Table 4*		
Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)		
	PP Analysis Group	
	Cipro XR	Cipro®
All Patients	N=197	N=221
Eradication	176 (89.3%)	188 (85.1%)
95% C. I. for Diff. in Prop. (weighted by infection type)	(-1.9%, 10.9%)	
AUP Patients	N=39	N=50
Eradication	34 (87.2%)	49 (98.0%)
97.5% C. I. for Diff. in Prop.	(-35.8%, 6.5%)	
cUTI Patients	N=158	N=171
Eradication	142 (89.9%)	139 (81.3%)
97.5% C. I. for Diff. in Prop.	(0.01%, 17.2%)	
<b>Breslow-Day test for treatment-by-infection-type interaction in PP group, p-value=0.006</b>		

\* Analysis groups defined according to original-protocol-defined TOC time window of within 5 and 9 days post-treatment.

#### 2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 5 displays the bacteriological response at the TOC time point by demographic variables.

Table 5: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Age and Race				
PP Analysis Group				
Eradication Rate	AUP Patients		cUTI Patients	
	Cipro XR	Cipro®	Cipro XR	Cipro®
All Patients	35/40 (88%)	51/52 (98%)	148/166 (89%)	144/177 (81%)
Age				
<65 years	30/34 (88%)	49/50 (98%)	55/66 (83%)	41/57 (72%)
65 to 74 years	4/5 (80%)	0/0 (NA)	38/39 (97%)	40/49 (82%)
≥75 years	1/1 (100%)	2/2 (100%)	55/61 (90%)	63/71 (89%)
Race				
Caucasian	20/24 (83%)	27/28 (96%)	128/144 (89%)	122/149 (82%)
Black	6/6 (100%)	8/8 (100%)	11/13 (85%)	14/19 (74%)
Asian	1/1 (100%)	0/0 (NA)	0/0 (NA)	1/1 (100%)
Hispanic	8/9 (89%)	16/16 (100%)	9/9 (100%)	7/8 (88%)
Gender				
Male	6/7 (86%)	9/9 (100%)	75/81 (93%)	72/93 (77%)
Female	29/33 (88%)	42/43 (98%)	73/85 (86%)	72/84 (86%)

In general, the difference between treatment groups within each demographic subcategory mirrors the trend observed for the primary efficacy analysis in the overall group. That is the Cipro XR group has a higher eradication rate than Cipro® within cUTI subjects and conversely, the Cipro® group has a higher eradication rate than Cipro XR within AUP subjects.

Since the treatment effect appears to be different for each infection type, the by-treatment group differences in eradication rates are considered within each stratum. The differences in eradication rates in AUP subjects between the two treatment groups were difficult to judge because of the small number of subjects in each subcategory but appeared to be fairly constant across age, race, and gender subcategories. In cUTI subjects, the difference in eradication rates between the two treatment groups was greatest in the age group 65 to 74 years (97% Cipro XR and 82% Cipro®). The differences in eradication rates in cUTI subjects between the two treatment groups were fairly constant across race. In cUTI subjects, the difference in eradication rates between the two treatment groups was largest for males (93% Cipro XR and 77% Cipro®).

Table 6 displays the bacteriological response at the TOC time point by organism and strata. The eradication rates appear to be numerically similar in the two treatment groups for each of the organisms.

Table 6: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Organism		
Eradication Rate in AUP Patients	PP Analysis Group	
	Cipro XR	Cipro®
Staphylococcus Aureus	0/0 (NA)	1/1 (100%)
Staphylococcus Saprophyticus	1/1 (100%)	1/1 (100%)
Enterococcus Faecalis	0/1 (0%)	5/6 (83%)
Escherichia Coli	35/36 (97%)	41/41 (100%)
Klebsiella Pneumoniae	2/2 (100%)	2/2 (100%)
Proteus Mirabilis	0/0 (NA)	3/3 (100%)
Citrobacter Koseri	0/0 (NA)	1/1 (100%)
Pseudomonas Aeruginosa	1/1 (100%)	0/0 (NA)
Weeksella Virosa	0/0 (NA)	1/1 (100%)
Eradication Rate in cUTI Patients	Cipro XR	Cipro®
Staphylococcus Aureus	4/6 (67%)	2/3 (67%)
Staphylococcus Saprophyticus	1/1 (100%)	1/1 (100%)
Enterococcus Faecalis	17/18 (94%)	14/21 (67%)
Enterococcus Faecium	1/2 (50%)	0/0 (NA)
Escherichia Coli	91/94 (97%)	90/92 (98%)
Klebsiella Pneumoniae	20/23 (87%)	19/23 (83%)
Klebsiella Oxytoca	1/1 (100%)	6/7 (86%)
Proteus Mirabilis	11/12 (92%)	10/11 (91%)
Enterobacter Cloacae	2/2 (100%)	3/3 (100%)
Enterobacter Aerogenes	4/4 (100%)	6/6 (100%)
Serratia Marcescens	2/2 (100%)	4/4 (100%)
Citrobacter Freundii	3/4 (75%)	4/4 (100%)
Citrobacter Koseri	1/1 (100%)	1/2 (50%)
Citrobacter Youngae	1/1 (100%)	0/0 (NA)
Morganella Morganii	0/0 (NA)	2/2 (100%)
Providencia Rettgeri	0/0 (NA)	2/2 (100%)
Pseudomonas Aeruginosa	3/3 (100%)	3/3 (100%)
Burkholderia Cepacia	1/1 (100%)	0/0 (NA)

## 2.5 STATISTICAL AND TECHNICAL ISSUES

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Consideration of “indeterminate” bacteriologic or clinical responses at TOC or follow-up (ref: *Section 2.3.1.1*)
- Redefinition of acceptable time window for collection of TOC efficacy data (ref: *Section 2.3.1.1 and 2.3.1.2*)
- Sample size revisions as a result of overestimating the validity rate, under estimating the eradication rate, and changing delta from 15% to 10% (ref: *Section 2.3.1.1*)
- Statistically significant treatment-by-infection-type interaction for primary efficacy endpoint (ref: *Section 2.3.1.2*)

- Statistically significantly more subjects excluded from PP analysis group for Cipro XR group than Cipro® group (ref: *Section 2.3.1.2*)

## 2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

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

*Within the cUTI stratum*, it is the opinion of this reviewer that Cipro XR has been shown to be noninferior to Cipro® for the bacteriological eradication rate at TOC endpoint in the PP analysis group. Disproportionately more subjects in the Cipro XR arm were excluded from the PP analysis group for no valid TOC urine culture (which most commonly was due to adverse event or protocol violation). The majority of these subjects were considered failures in the mITT analysis since their bacteriological response at TOC was likely missing or indeterminate. Within the cUTI stratum in the mITT group, the noninferiority criterion was not met.

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

These results for the primary endpoint within each of the strata are not dependent on the use of the amended TOC window rather than the one defined in the original protocol.

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

- The eradication rates at follow-up for the cUTI subjects were higher in the Cipro XR group than in the Cipro® group. Conversely, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro® group than in the Cipro XR group. These trends are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata.
- The clinical success rates at TOC for the cUTI subjects in the PP analysis group were slightly higher in the Cipro XR group than in the Cipro® group. The clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro® and Cipro XR groups in the PP analysis group. The Cipro XR group had slightly lower clinical success rates than the Cipro® group in the mITT analysis.
- The clinical success rates at the follow-up visit for the cUTI subjects in the PP analysis group were higher in the Cipro XR group than in the Cipro® group. Conversely, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR group than in the Cipro® group in the PP analysis group. Similar trends were

observed in the mITT analysis. These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint.

Examination of the primary efficacy endpoint by age, race, and gender indicated that in cUTI subjects, the difference in eradication rates between the two treatment groups was greatest in the age group 65 to 74 years. Also for cUTI subjects, the differences in eradication rates were fairly constant across races. And the difference in eradication rates was larger for males than females in cUTI subjects. The differences in eradication rates in AUP subjects between the two treatment groups were difficult to judge because of the small number of subjects in each subcategory but appeared to be fairly constant across age, race, and gender subcategories.

Tabulations of the bacteriologic success at the TOC visit were fairly numerically consistent across treatment groups for each of the organisms studied.

## 2.7 CONCLUSIONS AND RECOMMENDATIONS

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

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-554**

**Microbiology Review(s)**

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

**NDA#**: 21-554

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 29-OCT-02  
**CDER DATE:** 29-OCT-02  
**REVIEW ASSIGN DATE:** 30-OCT-02  
**REVIEW COMPLETE DATE:** 10-MAR-03

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

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

**SUBMISSION REVIEWED:** Original New Drug Application (CIPRO® XR)

**DRUG CATEGORY:** Antimicrobial: Fluoroquinolone

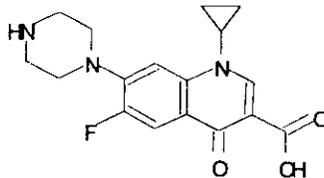
**INDICATIONS:** Complicated Urinary Tract Infections

**DOSAGE FORM:** 1000-mg Tablets

**DRUG PRODUCT NAME**

**PROPRIETARY:** CIPRO® XR  
**NONPROPRIETARY/USAN:** ciprofloxacin hydrochloride  
**CODE:** BAY q 3939  
**CHEMICAL NAME:** 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[1-piperazinyl]-3-quinolone-carboxylic acid

**STRUCTURAL FORMULA:**



**Molecular Formula:** C<sub>17</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub>  
**Molecular Weight:** 331.4

**SUPPORTING DOCUMENTS:**

IND #21,804—Bayer Ciprofloxacin Tablets  
IND #43,007—Bayer Ciprofloxacin Oral Suspension  
IND #25,173—Bayer Ciprofloxacin IV  
NDA #19-537—Bayer Ciprofloxacin Tablets—Approved October 22, 1987  
NDA #19-847—Bayer Ciprofloxacin IV 1%—Approved December 26, 1990  
NDA #19-857—Bayer Ciprofloxacin IV in 5% Dextrose—Approved December 26, 1990  
NDA #19-858—Bayer Ciprofloxacin IV in 0.9% Saline—Approved December 26, 1990  
NDA #20-780—Bayer Ciprofloxacin Oral Suspension—Approved September 26, 1997  
NDA #21-473—Bayer Ciprofloxacin XR Tablets (500 mg)—Approved December 13, 2002

**BACKGROUND:**

This application is for a new dosage (1000 mg) extended release tablet of ciprofloxacin. This new formulation is a once daily modified release tablet. This application requests indications of complicated urinary tract infections and acute uncomplicated pyelonephritis. The 500 mg extended release tablet formulation was approved in December, 2002 for uncomplicated urinary tract infections.

These ciprofloxacin extended release tablets are coated, two layer tablets containing both immediate-release and controlled-release components. Approximately 35% of the dose is provided by the immediate-release component and 65% by the slow-release matrix. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). The modified release tablets result in a higher  $C_{max}$  and an equivalent AUC when compared to Cipro® Tablets for the same total dose (e.g. Ciprofloxacin XR 1000 mg tablets compared to Cipro® 500 mg twice daily).

This application is for the indications of complicated urinary tract infections and acute uncomplicated pyelonephritis. One randomized, double-blind, controlled multicenter clinical trial (Study 100275) forms the basis of the clinical section of the application. This trial was performed in patients with complicated urinary tract infections and acute uncomplicated pyelonephritis and enrolled 1,042 patients. This trial compared ciprofloxacin XR 1000 mg tablets given once a day for 7 to 14 days with Cipro® 500 mg tablets given twice a day for 7 to 14 days.

**CONCLUSIONS:**

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The required microbiology revisions are listed as recommendations at the end of this review on pages 23-26.

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## EXECUTIVE SUMMARY

The applicant is requesting an indication of complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, *Enterobacter aerogenes* or *Pseudomonas aeruginosa* and uncomplicated acute pyelonephritis caused by *Escherichia coli*.

In Study 100275 CIPRO MR tablets (1000 mg once daily for 7-14 days) were compared with immediate-release ciprofloxacin tablets (500 mg twice daily for 7-14 days) in the treatment of complicated urinary tract infections or acute uncomplicated pyelonephritis. The primary endpoint was bacteriological eradication at 5-11 days post-therapy. The bacteriological eradication rate for CIPRO XR in acute uncomplicated pyelonephritis (AUP) was 87.5% (35/40) compared to 98.1% (51/52) for immediate release tablets. The bacteriological rate for CIPRO XR in complicated UTI was 89.2% (148/166) compared to 81.4% (144/177) for the immediate release tablets. The eradication rates for individual pathogens are shown in TABLE A.

TABLE A  
Bacteriological Eradication Rates at Test-of-Cure Visit

Pathogen	CIPRO XR (1000 mg QD)	Cipro Immediate Release (500 mg BID)
AUP Patients		
<i>Escherichia coli</i>	35/36 (97%)	41/41 (100%)
cUTI Patients		
<i>Escherichia coli</i>	91/94 (97%)	90/92 (98%)
<i>Klebsiella pneumoniae</i>	20/21 (95%)	19/23 (83%)
<i>Enterococcus faecalis</i>	17/17 (100%)	14/21 (67%)
<i>Proteus mirabilis</i>	11/12 (92%)	10/10 (100%)
<i>Enterobacter aerogenes</i>	4/4 (100%)	6/6 (100%)
<i>Pseudomonas aeruginosa</i>	3/3 (100%)	3/3 (100%)

As usual in urinary tract infections, most of the pathogens were *Escherichia coli*. There were very few of the other pathogens detected in the clinical trial. Eradication rates were good for all six of the listed pathogens. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*.

## PRECLINICAL EFFICACY (IN VITRO)

### MECHANISM OF ACTION

No new information has been submitted.

### IN VITRO ACTIVITY AGAINST RECENT CLINICAL ISOLATES FROM UTIS

#### SURVEILLANCE STUDIES

The [ ] Database [ ] provided national surveillance data for UTI isolates for the year 2001. More than 250 medical centers contributed to this database. TABLE 1 summarizes the *in vitro* activity of ciprofloxacin against the most common UTI pathogens during this time period.

TABLE 2  
Ciprofloxacin Surveillance Data for UTI Isolates ( Database—2001)

Organism	Total Number	% Susceptible	% Intermediate	% Resistant
<i>Citrobacter koseri</i>	2,947	98.0	0.1	1.9
<i>Citrobacter freundii</i>	4,377	85.3	2.5	12.2
[ ]	<b>3,843</b>	<b>95.7</b>	<b>0.6</b>	<b>3.7</b>
<i>Enterobacter cloacae</i>	5,224	85.1	1.7	13.2
<b><i>Escherichia coli</i></b>	<b>168,887</b>	<b>94.7</b>	<b>0.1</b>	<b>5.2</b>
<i>Klebsiella oxytoca</i>	3,348	91.5	1.3	7.2
<b><i>Klebsiella pneumoniae</i></b>	<b>28,181</b>	<b>95.3</b>	<b>0.6</b>	<b>4.2</b>
<b><i>Proteus mirabilis</i></b>	<b>16,871</b>	<b>84.5</b>	<b>1.3</b>	<b>14.2</b>
<i>Serratia marcescens</i>	1,743	84.6	3.2	12.2
<b><i>Pseudomonas aeruginosa</i></b>	<b>15,271</b>	<b>58.6</b>	<b>2.9</b>	<b>38.5</b>
<b><i>Enterococcus faecalis</i></b>	<b>11,872</b>	<b>61.4</b>	<b>5.4</b>	<b>33.2</b>
<i>Staphylococcus aureus</i> (MS)	3,523	81.9	1.4	16.7
<i>Staphylococcus saprophyticus</i>	826	98.7	0.2	1.1

MS = methicillin-susceptible

Bolded organisms are the ones proposed by the sponsor for the requested indication.

Over 90% of *Enterobacter aerogenes*, *Escherichia coli*, and *Klebsiella pneumoniae* isolates were susceptible to ciprofloxacin. Over 14% of *Proteus mirabilis* were resistant to ciprofloxacin. Over 30% of *Enterococcus faecalis* and *Pseudomonas aeruginosa* isolates were resistant to ciprofloxacin. *Enterococcus faecalis* is one of the organism listed under UTI in the present ciprofloxacin tablet label. It is listed in the microbiology subsection of the present ciprofloxacin tablet label with the qualifier that many strains are only moderately susceptible. This same qualifier is proposed for the labeling of this product. The percentages in the above table are based on breakpoints established for systemic infections. The amount

of ciprofloxacin in urine is much higher than in plasma, so ciprofloxacin should be effective in urinary tract infections against organisms that would appear to be resistant using these breakpoints.

An evaluation of the susceptibility of *Escherichia coli* in the nine U.S. Census regions showed that the susceptibility was similar in six of the nine regions; the susceptibility rate was 95.6% to 98% (TABLE 2). In the Mid Atlantic, South Atlantic, and West South Central regions, the ciprofloxacin susceptibility of *E. coli* was somewhat lower at 91.4% to 92.5%.

TABLE 2  
 Ciprofloxacin Surveillance Data for *E. coli* UTI Isolates /2001/By Region\*

Organism	Total Number	% Susceptible	% Intermediate	% Resistant
East North Central	27,674	96.0	0.1	3.9
East South Central	7,878	95.9	0	4.0
Mid Atlantic	24,188	92.3	0.1	7.6
Mountain	29,009	96.7	0.1	3.2
New England	3,739	98.0	0.1	2.0
Pacific	36,553	95.6	0.1	4.4
South Atlantic	21,267	91.4	0.2	8.4
West North Central	10,177	96.7	0	3.2
West South Central	10,820	92.5	0.1	7.4

[ ]<sup>TM</sup> Database— [ ]

It appears that the overall susceptibility to ciprofloxacin has decreased after 15 years of use; however, the majority of the organisms responsible for most complicated urinary tract infections remain susceptible to ciprofloxacin, especially when urine concentrations of the drug are considered.

#### DATA FROM THE CLINICAL STUDY

This application has one pivotal study 100275. This was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter trial to evaluate the efficacy and safety of Cipro XR tablets, 1000 mg once daily for 7 to 14 days. The comparative arm was a conventional immediate-release ciprofloxacin 500-mg tablet twice daily for 7 to 14 days. The trial was for the treatment of patients with complicated urinary tract infections (cUTI) or acute uncomplicated pyelonephritis (AUP). The primary endpoint for this clinical trial was bacteriological eradication at the test-of-cure visit (5 to 11 days after the completion of therapy). Secondary efficacy parameters were microbiological outcome at the late follow-up visit (Day 28 to 42) and clinical outcome at both visits.

During the clinical study the susceptibility of the causative organisms was determined at the central laboratory [ ]. Broth microdilution susceptibility tests were performed according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines. All causative organisms valid for efficacy from the Ciprofloxacin XR arm and ciprofloxacin immediate-release arm are listed in TABLE 3. *Escherichia coli* was the most frequently isolated organism (n=263), followed by *Klebsiella pneumoniae* (n=50), *Enterococcus faecalis* (n=46), and *Proteus mirabilis* (n=26). The MIC<sub>90</sub> for *E. coli* was 0.06 µg/mL, while the MIC<sub>90</sub> for *K. pneumoniae* and *P. mirabilis* were 0.5 µg/mL and 2 µg/mL, respectively. The MIC<sub>90</sub> for the other 46 isolates of Enterobacteriaceae was ≤1 µg/mL and the MIC<sub>90</sub> for *E. faecalis* was 2 µg/mL.

TABLE 3  
MICs of Pre-therapy Isolates in Ciprofloxacin XR and Cipro Immediate-Release Arms  
(Patients Valid for Efficacy)

Organism	Total Number	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)
<b>Urine</b>				
<i>Staphylococcus aureus</i>	10		0.25	0.5
<i>Staphylococcus saprophyticus</i>	4		0.25	0.25
<b><i>Enterococcus faecalis</i></b>	<b>46</b>		<b>1.0</b>	<b>2.0</b>
<i>Enterococcus faecium</i>	2		1.0	2.0
<b><i>Escherichia coli</i></b>	<b>263</b>		<b>0.015</b>	<b>0.06</b>
<b><i>Klebsiella pneumoniae</i></b>	<b>50</b>		<b>0.06</b>	<b>0.5</b>
<i>Klebsiella oxytoca</i>	8		0.015	0.5
<b><i>Proteus mirabilis</i></b>	<b>26</b>		<b>0.03</b>	<b>2.0</b>
<i>Enterobacter cloacae</i>	8		0.03	0.03
<b><i>Enterobacter aerogenes</i></b>	<b>10</b>		<b>0.03</b>	<b>0.06</b>
<i>Serratia marcescens</i>	6		0.06	1.0
<i>Citrobacter freundii</i>	8		0.015	0.12
<i>Citrobacter koseri</i>	4		0.008	0.5
<i>Citrobacter youngae</i>	1		0.015	0.015
<i>Morganella morganii</i>	2		0.015	0.015
<i>Providencia rettgeri</i>	2		0.03	0.03
<b><i>Pseudomonas aeruginosa</i></b>	<b>7</b>		<b>0.12</b>	<b>0.5</b>
<i>Burkholderia cepacia</i>	1		1.0	1.0
<i>Weeksella virosa</i>	1		1.0	1.0
<b>Blood</b>				
<b><i>Escherichia coli</i></b>	<b>11</b>		<b>0.015</b>	<b>0.12</b>
<b><i>Klebsiella pneumoniae</i></b>	<b>1</b>		<b>0.03</b>	<b>0.03</b>

TABLE 4 provides pre-therapy MIC data for all organisms isolated during the clinical trial for all patients valid for safety. The frequency of isolation of the organisms was about the same as that seen in the valid for efficacy population. The MIC<sub>90</sub> for 383 isolates of *Escherichia coli* was 0.25 µg/mL, while the MIC<sub>90</sub> for *K. pneumoniae* (n=76) and *P. mirabilis* (n=33) were 0.5 µg/mL and 2 µg/mL, respectively. The MIC<sub>90</sub> for the majority of other Enterobacteriaceae (n=49) were ≤0.5 µg/mL with the exception of *Serratia marcescens* (n=7) which had a MIC<sub>90</sub> of 16 µg/mL. The MIC<sub>90</sub> for 75 isolates of *E. faecalis* was 16 µg/mL. The MIC<sub>90</sub> for 15 isolates of *P. aeruginosa* was also 16 µg/mL.

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TABLE 4  
 MICs of Pre-therapy Isolates in Ciprofloxacin XR and Cipro Immediate-Release Arms  
 (Patients Valid for Safety)

Organism	Total Number	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)
<b>Urine</b>				
<i>Staphylococcus aureus</i>	16		0.5	16.0
<i>Staphylococcus saprophyticus</i>	6		0.25	0.25
<i>Enterococcus faecalis</i>	75		1.0	16.0
<i>Enterococcus faecium</i>	5		16.0	16.0
<i>Escherichia coli</i>	383		0.015	0.25
<i>Klebsiella pneumoniae</i>	76		0.03	0.5
<i>Klebsiella oxytoca</i>	12		0.03	0.06
<i>Proteus mirabilis</i>	33		0.03	2.0
<i>Enterobacter cloacae</i>	9		0.03	0.03
<i>Enterobacter aerogenes</i>	10		0.03	0.06
<i>Serratia marcescens</i>	7		0.06	16.0
<i>Serratia liquefaciens</i>	1		0.03	0.03
<i>Citrobacter freundii</i>	9		0.06	0.5
<i>Citrobacter koseri</i>	4		0.008	0.5
<i>Citrobacter youngae</i>	1		0.015	0.015
<i>Citrobacter brakii</i>	1		0.015	0.015
<i>Morganella morganii</i>	2		0.015	0.015
<i>Providencia stuartii</i>	1		4.0	4.0
<i>Providencia rettgeri</i>	2		0.03	0.03
<i>Pseudomonas aeruginosa</i>	15		0.25	16.0
<i>Burkholderia cepacia</i>	3		1.0	8.0
<i>Acinetobacter species</i>	1		4.0	4.0
<i>Acinetobacter xylosoxidans</i>	1		4.0	4.0
<i>Weeksella virosa</i>	1		1.0	1.0
<b>Blood</b>				
<i>Staphylococcus aureus</i>	1		0.12	0.12
<i>Staphylococcus saprophyticus</i>	1		0.25	0.25
<i>Enterococcus faecalis</i>	1		0.5	0.5
<i>Escherichia coli</i>	22		0.025	0.12
<i>Klebsiella pneumoniae</i>	2		0.03	0.06
<i>Acinetobacter species</i>	2		0.25	0.5

## PHARMACOKINETICS/BIOAVAILABILITY

The proposed dose is a single 1000-mg tablet taken once a day for 7 to 14 days.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following 1000 mg Ciprofloxacin XR once daily is 16.83 mg.h/L. This is about equal to the AUC for immediate-release ciprofloxacin 500 mg given twice daily. The peak plasma concentration ( $C_{max}$ ) of Ciprofloxacin XR 1000 mg is higher than that seen with the corresponding Ciprofloxacin 500 mg immediate-release tablet. Median time to maximum plasma concentration ( $t_{max}$ ) for Ciprofloxacin XR was 2.0 hours, which was comparable to that of immediate-release ciprofloxacin. The elimination half-lives for both formulations were approximately six hours. TABLE 4 compares the pharmacokinetic parameters at steady state for the two tablet formulations.

TABLE 4  
Ciprofloxacin Pharmacokinetics (Mean  $\pm$  Standard Deviation)

	$C_{max}$ (ug/mL)	AUC <sub>0-24h</sub> (mg.h/L)	T <sub>1/2</sub> (hours)	T <sub>max</sub> (hours)*
CIPRO XR 1000 mg QD	3.11 $\pm$ 1.08	16.83 $\pm$ 5.65	6.31 $\pm$ 0.72	2.0 (1-4)
CIPRO 500 mg BID	2.06 $\pm$ 0.41	17.04 $\pm$ 4.79	5.66 $\pm$ 0.89	2.0 (0.5-3.5)

\* median (range)

## RESULTS FROM CLINICAL TRIAL

### STUDY 100275

This was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter trial to evaluate the efficacy and safety of Cipro XR tablets, 1000 mg once daily for 7 to 14 days. The comparative arm was a conventional immediate-release ciprofloxacin 500-mg tablet twice daily for 7 to 14 days. The trial was for the treatment of patients with complicated urinary tract infections (cUTI) or acute uncomplicated pyelonephritis (AUP). The primary endpoint for this clinical trial was bacteriological eradication at the test-of-cure visit (5 to 11 days after the completion of therapy). Secondary efficacy parameters were microbiological outcome at the late follow-up visit (Day 28 to 42) and clinical outcome at both visits.

A total of 1042 patients were enrolled at 100 centers in the US and Canada. Of the 1042 enrolled patients, 521 were assigned to treatment with Cipro XR 1000 mg QD and 521 were assigned to treatment with Cipro 500 mg BID. Seven patients (4 in the Cipro XR group and 3 in the Cipro 500 mg BID group) were not included in the valid for safety population because study drug administration could not be documented. There were 517 (408 cUTI and 109 pyelonephritis) patients in the Cipro XR QD group and 518 (407 cUTI and 111 pyelonephritis) patients in the Cipro 500 mg BID group in the valid for safety population.

TABLE 5 displays the reasons for premature termination of the study. As seen in this table, 199 patients in the Cipro XR group and 91 patients in the Cipro BID group did not complete the study as planned. The most common reason for discontinuation was a protocol violation. The most common protocol violations were lack of causative organisms (i.e. no pretherapy pathogen recovered, organism recovered at  $<10^5$  CFU/mL, or no urine culture specimen obtained) or the presence of a resistant organism.

TABLE 5  
 Reasons for premature discontinuation of study drug

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

TABLE 6 presents a summary of the reasons for patients being excluded from the efficacy population.

TABLE 6  
 Reasons for exclusion from the efficacy population

	Cipro XR (N = 521)	Cipro BID (N = 521)
Any reason	315 (61%)	292 (56%)
No causative organism	175 (34%)	194 (37%)
No valid test-of-cure urine culture	76 (15%)	45 (9%)
Exclusion/inclusion criteria violation	21 (4%)	16 (3%)
Organism resistant to study drug	21 (4%)	15 (3%)
Protocol violation	9 (2%)	7 (1%)
Noncompliance with dosage regimen	5 (1%)	5 (1%)
Did not receive study drug	4 (1%)	3 (1%)
Inadequate duration of treatment	1 (0%)	4 (1%)
Posttherapy antibiotics	2 (<1%)	2 (<1%)
Concomitant antimicrobial therapy	1 (<1%)	1 (<1%)
Valid for efficacy	206 (39.5%)	229 (44%)

The Cipro BID group had a slightly higher rate of patients who had no causative organism. The Cipro XR group had a higher rate (15%) of patients who had no valid test-of-cure (TOC) urine culture result as compared to the Cipro BID group (9%). There were, therefore, four hundred thirty-five patients valid for efficacy—206 (166 cUTI; 40 AUP) in the Cipro XR group and 229 (177 cUTI; 52 AUP) in the Cipro BID group. TABLE 7 summarizes the microbiological outcome for the valid for efficacy patients at the TOC visit.

TABLE 7  
 Microbiological Outcome at the Test-of-Cure Visit  
 (Valid for Efficacy Population)

	Ciprofloxacin XR 1000 mg PO QD x 7-14 days	Cipro® 500 mg PO BID x 7-14 days
All Patients	N = 206	N = 229
Eradication (%)	183 (88.8%)	195 (85.2%)
Persistence (%)	10 (4.9%)	17 (7.4%)
Superinfection (%)	5 (2.4%)	3 (1.3%)
New Infection (%)	8 (3.9%)	14 (6.1%)
AUP Patients	N = 40	N = 52
Eradication (%)	35 (87.5%)	51 (98.1%)
Persistence (%)	2 (5.0%)	1 (1.9%)
New Infection (%)	3 (7.5%)	0
cUTI Patients	N = 166	N = 177
Eradication (%)	148 (89.2%)	144 (81.4%)
Persistence (%)	8 (4.8%)	16 (9.0%)
Superinfection (%)	5 (3.0%)	3 (1.7%)
New Infection (%)	5 (3.0%)	14 (7.9%)

When all patients are considered the eradication rates for Cipro XR and Cipro BID are about equal. The results of the treatment group comparisons between infection types were not consistent. Whereas the eradication rates for pyelonephritis patients was higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%), they were higher in the Cipro XR group (89.2%) than in the Cipro BID group (81.4%) in complicated UTI patients. The difference between patients with pyelonephritis and those with complicated UTI was caused primarily by the outcome of three pyelonephritis patients in the Cipro XR group who developed a new infection compared to zero patients in the Cipro BID group. All three cases of new infection were females between the ages of 18 and 21 years. All of the new infections were due to *Enterococcus faecalis* or *Enterococcus faecalis* and *Enterococcus faecium*. All three patients had a clinical response of cure at the TOC visit and only one patient had alternative treatment. All organisms were eradicated at the follow-up visit.

Results for the microbiological outcome at the late follow-up visit are summarized in TABLE 8.

TABLE 8  
 Microbiological Outcome at the Late Follow-Up Visit  
 (Valid for Efficacy Population)

	Ciprofloxacin XR 1000 mg PO QD x 7-14 days	Cipro® 500 mg PO BID x 7-14 days
All Patients	N = 206	N = 229
Continued Eradication	124 (60.2%)	115 (50.2%)
Eradication with Recurrence	19 (9.2%)	18 (7.9%)
Persistence	10 (4.9%)	17 (7.4%)
Superinfection	5 (2.4%)	2 (0.9%)
New Infection	21 (10.2%)	36 (15.7%)
Indeterminate	27 (13.1%)	41 (17.9%)
Continued Eradication Rate <sup>a</sup>	124/179 (69.3%)	115/188 (61.2%)
AUP Patients	N = 40	N = 52
Continued Eradication	25 (62.5%)	35 (67.3%)
Eradication with Recurrence	1 (2.5%)	3 (5.8%)
Persistence	2 (5.0%)	1 (1.9%)
New Infection	5 (12.5%)	4 (7.7%)
Indeterminate	7 (17.5%)	9 (17.3%)
Continued Eradication Rate <sup>a</sup>	25/33 (75.8%)	35/43 (81.4%)
CUTI Patients	N = 166	N = 177
Continued Eradication	99 (59.6%)	80 (45.2%)
Eradication with Recurrence	18 (10.8%)	15 (8.5%)
Persistence	8 (4.8%)	16 (9.0%)
Superinfection	5 (3.0%)	2 (1.1%)
New Infection	16 (9.6%)	32 (18.1%)
Indeterminate	20 (12.0%)	32 (18.1%)
Continued Eradication Rate <sup>a</sup>	99/146 (67.8%)	80/145 (55.2%)

<sup>a</sup> Continued Eradication rates do not include indeterminate responses

The Cipro XR group had a higher rate of continued eradication and lower rates of persistence and new infections, the Cipro BID group had a lower rate of superinfection. The rate of eradication with recurrence was similar in the two groups. Among patients with pyelonephritis, the continued eradication rate (not including indeterminate responses) was 76% (25/33) in the Cipro XR group and 81% (35/43) in the Cipro BID group. There was a higher rate of eradication with recurrence in the Cipro BID group (5.8%, as compared with 2.5% in the Cipro XR group), and more patients in this group than in the Cipro XR group developed a new infection during the follow-up period (2 in the Cipro XR group and 4 in the Cipro BID group).

TABLE 9 shows the microbiological results by pathogen at the TOC visit for the organisms proposed for this indication in the label.

TABLE 9  
 Bacteriological Eradication Rates at Test-of-Cure  
 (Patients Valid for Efficacy)

Organism	Cipro XR			Cipro BID		
	Erad (%)	Pers (%)	Indeter (%)	Erad (%)	Pers (%)	Indeter (%)
AUP Patients						
<i>Escherichia coli</i>	35 (97%)	1 (3%)	0	41 (100%)	0	0
cUTI Patients						
<i>Escherichia coli</i>	91 (97%)	3 (3%)	0	90 (98%)	2 (2%)	0
<i>Klebsiella pneumoniae</i>	20 (87%)	1 (4%)	2 (9%)	19 (83%)	4 (17%)	0
<i>Enterococcus faecalis</i>	17 (94%)	0	1 (6%)	14 (67%)	7 (33%)	0
<i>Proteus mirabilis</i>	11 (92%)	1 (8%)	0	10 (91%)	0	1 (9%)
<i>Pseudomonas aeruginosa</i>	4 (100%)	0	0	6 (100%)	0	0
Blood						
AUP Patients						
<i>Escherichia coli</i>	4 (80%)	0	1 (20%)	3 (75%)	0	1 (25%)
<i>Klebsiella pneumoniae</i>	1 (100%)	0	0	0	0	0
cUTI Patients						
<i>Escherichia coli</i>	1 (100%)	0	0	1 (100%)	0	0

Erad = eradication; Pers = persistence; Indeter = Indeterminate

The eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. Eradication rates for *Escherichia coli*, by far the most common organism, were high for both treatment groups. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*.

TABLE 10 presents a summary of the organisms causing superinfections or new infections in patients valid for efficacy. In the Cipro XR group, 5 patients had organisms that caused superinfections and 8 patients had organisms that caused new infection. In the Cipro BID group, 3 patients had organisms that caused superinfection and 14 patients had organisms that caused new infection. *Enterococcus faecalis* was the organism causing new infection in 7 patients in the Cipro XR group and 6 patients in the Cipro BID group. *Staphylococcus aureus* was the organism causing superinfection in the 3 patients in the Cipro XR group and new infection in 1 patient in the Cipro XR group and 4 patients in the Cipro BID group.

TABLE 10  
 Organisms Causing Superinfections or New Infections at TOC  
 (Patients Valid for Efficacy)

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

The number of organisms causing super or new infection is higher than patients with bacteriological response of super or new infection; this is due to some patients having persisting organisms and super or new infections. The patient response for these patients is persistence, but the super or new infecting organism is still shown in this table.

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TABLE 11 presents the bacteriological response rates by pathogen at the follow-up visit for the organisms proposed for this indication in the label.

TABLE 11  
 Bacteriological Eradication Rates at Follow-up (28 to 42 days posttreatment)  
 (Patients Valid for Efficacy)

Organism	Cipro XR				Cipro BID			
	Erad (%)	Recurr (%)	Pers (%)	Indeter (%)	Erad (%)	Recurr (%)	Pers (%)	Indeter (%)
AUP Patients								
<i>Escherichia coli</i>	27 (75%)	0	1 (3%)	8 (22%)	33 (80%)	1 (2%)	0	7 (17%)
cUTI Patients								
<i>Escherichia coli</i>	74 (79%)	10 (11%)	3 (3%)	7 (7%)	60 (65%)	10 (11%)	2 (2%)	20 (22%)
<i>Klebsiella pneumoniae</i>	13 (57%)	2 (9%)	1 (4%)	7 (30%)	12 (52%)	0	4 (17%)	7 (30%)
<i>Enterococcus faecalis</i>	10 (56%)	2 (11%)	0	6 (33%)	7 (33%)	2 (10%)	7 (33%)	5 (24%)
<i>Proteus mirabilis</i>	9 (75%)	1 (8%)	1 (8%)	1 (8%)	6 (55%)	2 (18%)	0	3 (27%)
[ ]	3 (75%)	0	0	1 (25%)	3 (50%)	0	0	3 (50%)
<i>Pseudomonas aeruginosa</i>	1 (33%)	1 (33%)	0	1 (33%)	1 (33%)	1 (33%)	0	1 (33%)
Blood								
AUP Patients								
<i>Escherichia coli</i>	4 (80%)	0	0	1 (20%)	3 (75%)	0	0	1 (25%)
<i>Klebsiella pneumoniae</i>	1 (100%)	0	0	0	0	0	0	0
cUTI Patients								
<i>Escherichia coli</i>	1 (100%)	0	0	0	1 (100%)	0	0	0

Erad = continued eradication; Recurr = eradication with recurrence; Pers = persistence; Indeter = Indeterminate

The eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*.

Organisms isolated at the follow-up visit that caused new infections in patients valid for efficacy are presented in TABLE 12. Of the 39 new infecting organisms recovered after the test-of-cure (TOC) visit, 18 were identified as *Enterococcus faecalis* (7 from patients in the Cipro XR group and 11 from patients in the Cipro BID group), 7 were identified as *Escherichia coli* (4 and 3, respectively), and 7 were identified as *Klebsiella pneumoniae* (0 and 7, respectively). There were more patients in the Cipro BID group than in the Cipro XR group who had new infecting organisms isolated between the TOC and follow-up visits (17 in the Cipro XR group versus 26 in the Cipro BID group).

TABLE 12  
Organisms Causing New Infections at Follow-Up (after TOC Visit)  
(Patients Valid for Efficacy)

Organism	Cipro XR	Cipro BID
New Infection		
<i>Staphylococcus aureus</i>	2	0
<i>Staphylococcus saprophyticus</i>	1	0
<i>Enterococcus species</i>	0	1
<i>Enterococcus faecalis</i>	7	11
<i>Escherichia coli</i>	4	3
<i>Klebsiella pneumoniae</i>	0	7
<i>Klebsiella oxytoca</i>	1	0
<i>Citrobacter freundii</i>	1	1
<i>Citrobacter amalonaticus</i>	0	1
<i>Pseudomonas aeruginosa</i>	1	2

The number of organisms causing super or new infection is higher than patients with bacteriological response of super or new infection; this is due to some patients having persisting organisms and super or new infections. The patient response for these patients is persistence, but the super or new infecting organism is still shown in this table.

Four hundred twenty-nine of the 435 valid for efficacy patients had a pretherapy blood culture obtained. Twelve of these 429 patients had bacteremia caused by *E. coli* (11 patients) and *K. pneumoniae* (1 patient). Ten of the twelve patients had subsequent blood cultures performed at the during-therapy visit; blood cultures were missing for the remaining two bacteremic patients. The infecting organism in the blood was eradicated in all 10 of the 12 patients who had blood culture results. These blood isolates are included in TABLES 13 and 14.

TABLE 13 shows the bacteriological response for the acute pyelonephritis patients by MIC value. TABLE 14 shows the same data for the complicated urinary tract infection patients (cUTI). Persistence was not associated with elevated MICs for any of the organisms.

TABLE 13  
 Microbiological Responses by MIC—AUP Patients (Patients Valid for Efficacy)

Organism	MIC ( $\mu\text{g/mL}$ )	Outcome	Ciprofloxacin MR 500 mg QD		Ciprofloxacin 250 mg BID	
			Number	%	Number	%
<b>AUP Patients—Urine</b>						
<i>Escherichia coli</i>	0.008	Eradication	1	100	3	100
	0.015	Eradication	24	96	25	100
		Persistence	1	4	0	0
	0.03	Eradication	6	100	7	100
	0.06	Eradication	2	100	2	100
	0.12	Eradication	1	100	1	100
	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	2	100
	ALL	Eradication	35	97	41	100
		Persistence	1	3	0	0
<b>AUP Patients--Blood</b>						
<i>Escherichia coli</i>	0.015	Eradication	4	80	0	0
		Indeterminate	1	20	1	100
	0.03	Eradication	0	0	1	100
	0.12	Eradication	0	0	1	100
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	80	3	75
		Indeterminate	1	20	1	25
<i>Klebsiella pneumoniae</i>	0.03	Eradication	1	100	0	0
	ALL	Eradication	1	100	0	0

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TABLE 14  
 Microbiological Responses by MIC—cUTI Patients (Patients Valid for Efficacy)

cUTI Patients--Urine						
<i>Escherichia coli</i>	0.008	Eradication	10	100	6	100
		Persistence	0	0	0	0
	0.015	Eradication	54	98	50	98
		Persistence	1	2	1	2
	0.03	Eradication	19	100	24	100
	0.06	Eradication	4	80	3	100
		Persistence	1	20	0	0
	0.12	Eradication	0	0	5	100
	0.25	Eradication	2	100	1	50
		Persistence	0	0	1	50
	0.5	Eradication	2	67	0	0
		Persistence	1	33	0	0
	1.0	Eradication	0	0	1	100
	ALL	Eradication	91	97	90	98
Persistence		3	3	2	2	
<i>Enterococcus faecalis</i>	0.25	Eradication	0	0	1	50
		Persistence	0	0	1	50
	0.5	Eradication	6	100	3	50
		Persistence	0	0	3	50
	1	Eradication	11	100	8	89
		Persistence	0	0	1	11
	2	Eradication	0	0	2	50
		Persistence	0	0	2	50
		Indeterminate	1	100	0	0
	ALL	Eradication	17	94	14	67
		Persistence	0	0	7	33
		Indeterminate	1	6	0	0
<i>Klebsiella pneumoniae</i>	0.015	Eradication	1	100	1	100
	0.03	Eradication	4	67	10	83
		Persistence	0	0	2	17
		Indeterminate	2	33	0	0
	0.06	Eradication	5	83	4	67
		Persistence	1	17	2	33
	0.12	Eradication	2	100	1	100
	0.25	Eradication	4	100	0	0
	0.5	Eradication	2	100	2	100
	1.0	Eradication	2	100	1	100
	ALL	Eradication	20	87	19	83
		Persistence	1	4	4	17
Indeterminate		2	9	0	0	

TABLE 14 (Continued)  
 Microbiological Responses by MIC—cUTI Patients (Patients Valid for Efficacy)

Organism	MIC ( $\mu\text{g/mL}$ )	Outcome	Ciprofloxacin MR 500 mg QD		Ciprofloxacin 250 mg BID	
			Number	%	Number	%
<i>Proteus mirabilis</i>	0.015	Eradication	2	100	0	0
	0.03	Eradication	5	100	5	100
	0.06	Eradication	3	75	1	100
		Persistence	1	25	0	0
	0.12	Eradication	0	0	1	100
	0.5	Indeterminate	0	0	1	100
	1	Eradication	1	100	0	0
	2	Eradication	0	0	3	100
	ALL	Eradication	11	92	10	91
		Persistence	1	8	0	0
Indeterminate		0	0	1	9	
<i>Enterobacter aerogenes</i>	0.015	Eradication	1	100	1	100
	0.03	Eradication	1	100	4	100
	0.06	Eradication	2	100	0	0
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	100	6	100
<i>Pseudomonas aeruginosa</i>	0.12	Eradication	2	100	2	100
	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	0	0
	ALL	Eradication	3	100	3	100
<b>cUTI Patients—Blood</b>						
<i>Escherichia coli</i>	0.015	Eradication	1	100	0	0
	0.12	Eradication	0	0	1	100
	ALL	Eradication	1	100	1	100

The patients valid for efficacy who were bacteriological persisters or clinical failures are shown in TABLE 15. More bacteriological persisters and clinical failures were seen in the Cipro BID arm (n = 26) compared with the Cipro XR arm (n = 15).

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TABLE 15  
Patients with Bacteriological Persistence or Clinical Failure

Patient #	Treatment	Organism	Cipro MIC	Bact Resp At TOC	Bact Resp At FU	Clin Resp At TOC	Clin Resp At FU
15005	Cipro XR	<i>E. coli</i>	0.06	Persistence	Persistence	Cure	
31006	Cipro XR	<i>P. mirabilis</i>	0.06	Persistence	Persistence	Cure	Relapse
31012	Cipro XR	<i>E. faecalis</i>	1.0	Eradication	Indeterminate	Failure	Failure
42012	Cipro XR	<i>S. aureus</i>	2.0	Persistence	Persistence	Cure	
42056	Cipro XR	<i>C. freundii</i>	0.12	Persistence	Persistence	Failure	Failure
48037	Cipro XR	<i>S. aureus</i>	0.25	Persistence	Persistence	Cure	
49061	Cipro XR	<i>E. coli</i>	0.5	Persistence	Persistence	Cure	Con. Cure
73042	Cipro XR	<i>K. pneumoniae</i>	0.25	Eradication	Indeterminate	Failure	Failure
77018	Cipro XR	<i>E. coli</i>	0.015	Persistence	Persistence	Relapse	Relapse
98001	Cipro XR	<i>K. pneumoniae</i>	0.06	Persistence	Persistence	Cure	Failure
125006	Cipro XR	<i>K. pneumoniae</i>	0.25	Eradication	Indeterminate	Failure	Failure
127001	Cipro XR	<i>E. faecalis</i>	2.0	Indeterminate	Indeterminate	Failure	Failure
127001	Cipro XR	<i>K. pneumoniae</i>	0.03	Indeterminate	Indeterminate	Failure	Failure
209029	Cipro XR	<i>E. coli</i>	0.015	Persistence	Persistence	Cure	Relapse
209039	Cipro XR	<i>E. faecalis</i>	1.0	Persistence	Persistence	Failure	Failure
12002	Cipro BID	<i>E. coli</i>	0.015	Eradication	Indeterminate	Failure	Failure
13017	Cipro BID	<i>E. faecalis</i>	1.0	Persistence	Persistence	Cure	Con. Cure
15011	Cipro BID	<i>K. pneumoniae</i>	0.03	Persistence	Persistence	Cure	Relapse
25005	Cipro BID	<i>K. oxytoca</i>	0.5	Persistence	Persistence	Cure	Relapse
25029	Cipro BID	<i>E. faecalis</i>	1.0	Persistence	Persistence	Cure	Con. Cure
25029	Cipro BID	<i>E. coli</i>	0.03	Eradication	Con. Erad	Cure	Con. Cure
42038	Cipro BID	<i>C. koseri</i>	0.5	Persistence	Persistence	Cure	Failure
45019	Cipro Bid	<i>E. faecalis</i>	0.5	Persistence	Persistence		
48013	Cipro BID	<i>E. coli</i>	0.03	Eradication	Indeterminate	Failure	Failure
53029	Cipro BID	<i>K. pneumoniae</i>	0.06	Eradication	Persistence	Failure	Failure
59033	Cipro BID	<i>K. pneumoniae</i>	0.5	Eradication	Indeterminate	Failure	Failure
73046	Cipro BID	<i>E. faecalis</i>	0.25	Persistence	Persistence	Cure	Con. Cure
73046	Cipro BID	<i>E. coli</i>	0.015	Eradication	Con Erad	Cure	Con. Cure
74015	Cipro BID	<i>K. pneumoniae</i>	0.03	Persistence	Persistence	Failure	Failure
76011	Cipro BID	<i>K. pneumoniae</i>	0.06	Persistence	Persistence	Failure	Failure
77006	Cipro BID	<i>E. coli</i>	0.015	Persistence	Persistence		
91008	Cipro BID	<i>E. coli</i>	0.25	Persistence	Persistence	Failure	Failure
92011	Cipro BID	<i>E. faecalis</i>	1.0	Eradication	Indeterminate	Failure	Failure
92011	Cipro BID	<i>S. marcescens</i>	1.0	Eradication	Indeterminate	Failure	Failure
97001	Cipro BID	<i>S. aureus</i>	0.5	Persistence	Persistence	Relapse	Relapse
101007	Cipro BID	<i>E. faecalis</i>	2.0	Persistence	Persistence	Cure	
106019	Cipro BID	<i>K. pneumoniae</i>	0.03	Eradication	Indeterminate	Failure	Failure
127006	Cipro BID	<i>E. faecalis</i>	0.5	Persistence	Persistence	Failure	Failure
129001	Cipro BID	<i>E. faecalis</i>	2.0	Persistence	Persistence	Failure	Failure
133008	Cipro BID	<i>E. coli</i>	0.03	Eradication	Indeterminate	Failure	Failure
201006	Cipro BID	<i>E. faecalis</i>	0.5	Persistence	Persistence	Failure	Failure

Cipro = ciprofloxacin; Bact Resp = bacteriological response; Clin Resp = clinical response

TOC = test-of-cure; FU = follow-up

Con. Cure = continued cure; Con. Erad. = continued eradication

Isolates that had a MIC at post-therapy that was more than one dilution greater than the pretherapy MIC are presented in TABLE 16. Of 65 isolates from either the Cipro XR or Cipro BID arm, 11 isolates had elevated MICs at the Test-of-Cure (TOC) visit. The six isolates that were in the Cipro XR arm included *Escherichia coli* (n = 4), *Klebsiella pneumoniae* (n = 1), and *Staphylococcus aureus* (n = 1). The MICs of 2 isolates of *Escherichia coli* increased to 16 µg/mL; however, the organisms were eradicated at the TOC visit, but recurred at the follow-up visit. The MIC of one isolate of *E. coli* increased from 0.015 to 0.12 µg/mL and was not eradicated and the MIC of the other isolate, which recurred at the follow-up visit, increased from 0.03 to 0.5 µg/mL. The MIC of the isolate of *K. pneumoniae* increased from 0.06 to 0.5 µg/mL, while the MIC of the isolate of *S. aureus* increased from 2 to 16 µg/mL. Neither organism was eradicated. Similar results were seen in the Cipro BID arm. The development of resistance during therapy was low.

TABLE 16  
 Organisms with Elevated MICs (µg/mL) at Posttherapy<sup>a</sup>

Organism (No.)	MIC (µg/mL)		Eradication	
	Pre-Therapy	Post-Therapy	TOC	FU
<i>Escherichia coli</i>				
Cipro XR Arm (4)	0.015	0.12	No	No
	0.03	0.5	Yes	Recurred
	0.03	16	Yes	Recurred
	0.06	16	Yes	Recurred
Cipro BID Arm (3)	0.015	0.5	Yes	Recurred
	0.015	1.0	Yes	Recurred
	0.015	16	No	No
<i>Enterococcus faecalis</i>				
Cipro BID Arm (2)	0.5	2	No	No
	1	16	No	No
<i>Klebsiella pneumoniae</i>				
Cipro XR Arm (1)	0.06	0.5	No	No
<i>Staphylococcus aureus</i>				
Cipro XR Arm (1)	2	16	No	No

<sup>a</sup> MIC at post-therapy greater than one dilution higher than MIC at pre-therapy

## LABELING

The Microbiology subsection of the proposed label closely follows the label for ciprofloxacin tablets. Only organisms indicated for UTI have been placed in the clinical and *in vitro* activity listing (list #1). List #2 (*in vitro* activity only) has organisms that are listed in the ciprofloxacin tablet label. All the Gram-negative microorganisms are appropriate since they may be associated with UTI infections. The applicant has also listed [ ] and [ ] These two Gram-positive organisms are usually not associated with UTI infections and should, therefore, be deleted. ]

The susceptibility testing section is basically identical to that in the ciprofloxacin tablet label, but has been amended to include only the sections pertinent to organisms that are indicated for UTI infections. The statement that introduces the interpretive criteria should be revised to state what organisms the criteria are for rather than what organisms the criteria are not appropriate for. The revised labeling, which should be sent to the applicant, is presented at the end of this review under RECOMMENDATIONS on pages 23-26.

## RECOMMENDATIONS (To Be Communicated to Sponsor)

The sponsor should be notified of the following:

1. [ ] should be deleted from the listing of organisms with *in vitro* activity (list #2). These organisms are not usually associated with UTI infections.
2. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa* in the clinical trial. The Medical Officer will have to decide whether enough evidence was presented to allow these organisms into the clinical efficacy listing (list #1). If allowed they should be listed in alphabetical order.
3. In the Susceptibility Tests subsection the two sentences that read [ ] testing [ ] should be revised to read "For [ ]
4. The [ ] should be deleted from both susceptibility testing sections unless this organism is allowed in the indications.
5. The following statement should be added to the Diffusion Techniques subsection:  
"Interpretation should be as stated above for results using dilution techniques.  
Interpretation involves correlation of the diameter obtained in the disk test with the MIC for [ ] [ ]

3 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

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Peter A. Dionne  
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir _____	Signature _____	Date _____
HFD-590/TLMicro _____	Signature _____	Date _____

CC:

HFD-590/Original NDA # 21-554  
HFD-590/Division File  
HFD-590/Micro/PDionne  
HFD-590/MO/JMeyer  
HFD-590/BioPham/DChilukuri  
HFD-520/Pharm/SHundley  
HFD-590/Chem/DMatecka  
HFD-590/CSO/JSaliba

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Peter Dionne  
4/18/03 01:54:48 PM  
MICROBIOLOGIST

Shukal signed 4/11/03--Ken signed 4/14/03

Shukal Bala  
4/22/03 03:50:22 PM  
MICROBIOLOGIST

Kenneth Hastings  
4/24/03 07:44:52 AM  
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-554**

**Clinical Pharmacology and Biopharmaceutics  
Review**

**Office of Clinical Pharmacology and Biopharmaceutics Review**

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<b>NDA</b>	21-554
<b>Generic</b>	Ciprofloxacin
<b>(Brand<sup>®</sup>)</b>	CIPRO <sup>®</sup> XR
<b>Dosage Strength</b>	1000 mg
<b>Submission Date</b>	October 29, 2002
<b>Applicant</b>	Bayer
<b>Clinical Division</b>	DSPIDP (HFD-590)
<b>OCPB Division</b>	DPE3 (HFD-880)
<b>Type of Submission</b>	NDA original submission
<b>Reviewer</b>	Dakshina Chilukuri, Ph.D.
<b>Pharmacometrics Reviewer</b>	Jenny J. Zheng, Ph.D.
<b>Team Leader</b>	Philip Colangelo, Ph.D.
<b>Review Date</b>	July 11, 2003

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**EXECUTIVE SUMMARY**

The applicant is seeking approval of CIPRO<sup>®</sup> XR (ciprofloxacin hydrochloride and ciprofloxacin\*) tablets containing 1000 mg ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration in NDA 21-554. CIPRO<sup>®</sup> XR Tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The proposed indications are treatment of complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, *L* or *Pseudomonas aeruginosa* and acute uncomplicated Pyelonephritis caused by *Escherichia coli*. The dosage regimen for complicated urinary tract infection and acute uncomplicated Pyelonephritis is CIPRO XR 1000 mg once-daily for 7-14 days.

CIPRO<sup>®</sup> XR 1000 mg is a *L* tablet formulation of ciprofloxacin. A lower strength of CIPRO<sup>®</sup> XR (500 mg) was approved in NDA 21-473 for the treatment of uncomplicated urinary tract infections (Acute Cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, or *Staphylococcus saprophyticus*. Ciprofloxacin is bactericidal at concentrations only two to four-fold above its bacteriostatic concentrations. Its bactericidal action results from inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, which are enzymes required for bacterial DNA replication, transcription, repair and recombination.

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

A total of 5 clinical pharmacology studies were conducted with CIPRO<sup>®</sup> XR 1000 mg in healthy volunteers. These studies compared pharmacokinetics of the CIPRO<sup>®</sup> XR 1000 mg once-daily regimen to the corresponding immediate release regimen (eg, 1000 mg XR vs. 500 mg immediate release BID) and examined the effects of food on the performance of the XR tablet. In addition, the drug interaction studies to study the effect of Maalox

and Omeprazole on the pharmacokinetics of CIPRO<sup>®</sup> XR were also conducted. These studies were reviewed in NDA 21-473 as part of the CIPRO<sup>®</sup> XR 500 mg tablet formulation.

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

Dosage adjustments for patients with renal impairment based on the Monte-Carlo simulations are acceptable. Additional simulations are recommended to confirm the applicant's proposed dosage adjustments and are listed below.

Based on the efficacy and safety results, the medical officer recommends approval for the CIPRO<sup>®</sup> XR 1000 mg tablets.

#### RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in original NDA 21-554 for CIPRO<sup>®</sup> XR. The Human Pharmacokinetics and Bioavailability Section of NDA 21-554 has met the requirements of the 21 CFR 320 and the clinical pharmacology labeling requirements of 21 CFR 201.56.

**Dissolution:** Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method for the tablet (USP Apparatus 2, rotation speed of 50 rpm, and dissolution medium of 0.1N HCl), is acceptable. The acceptance criteria for dissolution proposed by the applicant are acceptable and are given below:

30 minutes: L 1%  
60 minutes: L 1%  
120 minutes: Not Less Than L 1%

#### Dosage adjustments for renal impairment: Monte-Carlo simulations:

1. It appears the applicant used FO method in the modeling and simulation. It is known that FOCE/INTERACTION method is preferable for a relatively dense data set. Please address why only FO was used.
2. In the simulation, according to the code, CL<sub>cr</sub> of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renally impaired and severely renal impaired, respectively. This approach is considered to be inadequate. It

is preferable to simulate with ranges of  $CL_{cr}$  values for normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment. Therefore, as a Phase IV commitment, please perform additional Monte-Carlo simulations to obtain estimates of ciprofloxacin systemic exposure after administration of the following regimens:

- 1000 mg CIPRO<sup>®</sup> XR for 14 days in patients with mild renal impairment ( $CL_{cr}$  ~ 50 mL/min)
- 1000 mg CIPRO<sup>®</sup> XR for 14 days in patients with moderate renal impairment ( $CL_{cr}$  ~ 30 mL/min)
- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with severe renal impairment ( $CL_{cr}$  <30 mL/min)
- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with mild renal impairment ( $CL_{cr}$  ~ 50 mL/min)
- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with moderate renal impairment ( $CL_{cr}$  ~ 30 mL/min)
- 750 mg CIPRO<sup>®</sup> IR bid for 14 days in patients with normal renal function ( $CL_{cr}$  ~ 120 mL/min)

Based on the information obtained from the above-mentioned simulations, adjustments to the dosage regimen for CIPRO<sup>®</sup> XR 1000 mg in patients with mild and/or moderate renal impairment may be needed.

3. The applicant used the established relationship between clearance (CL) of intravenously administered ciprofloxacin and creatinine clearance ( $CL_{cr}$ ). However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of the orally administered Cipro IR tablet and use it for the purpose of modeling and simulations. We recommend that the applicant re-develop the relationship between oral ciprofloxacin clearance and creatinine clearance ( $CL_{cr}$ ) and compare with the previous results.

**Labeling:** The proposed label for ciprofloxacin XR tablets with the Clinical Pharmacology and Biopharmaceutics reviewer comments is attached as Appendix-1.

**Phase IV commitments:** The applicant is asked to address the following as Phase IV commitments:

Please perform additional Monte-Carlo simulations to obtain estimates of systemic exposure after administration of the following regimens:

- 1000 mg CIPRO<sup>®</sup> XR for 14 days in patients with mild renal impairment ( $CL_{cr}$  ~ 50 mL/min)
- 1000 mg CIPRO<sup>®</sup> XR for 14 days in patients with moderate renal impairment ( $CL_{cr}$  ~ 30 mL/min)
- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with severe renal impairment ( $CL_{cr}$  <30 mL/min)

- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with mild renal impairment ( $CL_{cr}$  — mL/min)
- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with moderate renal impairment ( $CL_{cr}$  — -50 mL/min)
- 750 mg CIPRO<sup>®</sup> IR bid for 14 days in patients with normal renal function ( $CL_{cr}$  — 120 mL/min)

/S/

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

/S/

Initialed by Philip Colangelo, Ph.D.  
cc: NDA 21-554, HFD-590, HFD-880 and CDR (Biopharm).

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## SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

### Single-dose and steady-state pharmacokinetics of CIPRO 1000 mg XR tablet vs. 500 mg IR tablet

The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of the CIPRO 1000 mg XR formulation to healthy subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation. The PK parameters observed following administration of CIPRO XR 1000 mg were comparable to the parameters observed following administration of Cipro IR 500 mg bid.

### Effect of food (pilot study) on pharmacokinetics of ciprofloxacin CIPRO 1000 mg XR tablet

The applicant compared the safety, tolerability and pharmacokinetics of the new CIPRO 1000 mg XR formulation given after a standard breakfast (4 slices toast, 20g butter, 50g jam, 20g cheese, 200mL decaffeinated coffee, 3g sugar) and after an overnight fast in comparison to the marketed immediate release ciprofloxacin product, given orally according to the bid dosing schedule as two doses of 500 mg to healthy subjects. After single dose administration of CIPRO 1000 mg XR ciprofloxacin tablet to fasted healthy subjects, the relative bioavailability ( $AUC_{0-24}$ ) of ciprofloxacin was 96% and the 90% CI lay within the bioequivalence criteria compared with 500 mg bid IR tablet. However,  $C_{max}$  was significantly greater by 89% for the XR formulation compared to the 500 mg IR tablet. No effect of food on the exposure of ciprofloxacin was observed.

### Effect of a high calorie, high fat meal on the pharmacokinetics of ciprofloxacin 1000 mg XR tablet

The applicant evaluated the effect of a high calorie, high fat meal (250 mL whole milk, 2 slices toast, 2 scrambled eggs, 3 slices fried ham, 125g hash brown potatoes, 20g butter and 2 cups decaffeinated coffee- providing a total of 977 Kcal) on the pharmacokinetics of CIPRO<sup>®</sup> XR 1000 mg formulation in healthy subjects. The CIPRO<sup>®</sup> XR formulation was found to be bioequivalent when administered under fasted and high fat, high calorie fed conditions. Hence, food does not appear to affect the rate or extent of ciprofloxacin exposure.

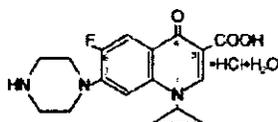
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## QUESTION BASED REVIEW

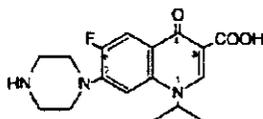
### General Attributes

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

CIPRO<sup>®</sup> XR tablets contain ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO<sup>®</sup> 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  $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$  and its molecular weight is 385.8. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is  $C_{17}H_{18}FN_3O_3$  and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



The composition of the commercial tablet formulation is as follows:

Ingredient	Amount (mg/tablet)
<b>IR -Layer</b>	
Ciprofloxacin hydrochloride	
(Ciprofloxacin betaine)	
Crospovidone	
Magnesium stearate	
Silica colloidal anhydrous	
<b>CR -Laver</b>	
Ciprofloxacin hydrochloride	
(Ciprofloxacin betaine)	

[	]	
Hypromellose		
Magnesium stearate		
Silica colloidal anhydrous		
<b>Film Coat</b>		
Hypromellose		
Polyethylene glycol		
Titanium dioxide		J
Total Weight		1513 mg

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

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

**What is the proposed dosage and route of administration?**

In complicated urinary tract infections and in acute uncomplicated pyelonephritis, the recommended dosage of CIPRO<sup>®</sup> XR is 1000 mg once daily for 7-14 days.

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

CIPRO XR (1000 mg once daily for 7 to 14 days) was evaluated for the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis in a large, randomized, double-blind, controlled clinical trial conducted in the US and Canada. This study compared CIPRO XR with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days) and enrolled 1,042 patients. The primary endpoint for this trial was bacteriological eradication at 5 to 11 days post-therapy for all patients evaluable for efficacy. The bacteriological eradication rate for CIPRO XR was 88.8% (183/206) compared to 85.2% (195/229) for immediate-release ciprofloxacin.

<u><b>PATHOGEN</b></u>	<u><b>CIPRO XR 1000 mg OD</b></u>	<u><b>Immediate-Release Ciprofloxacin 500 mg BID</b></u>
<i>Escherichia coli</i>	97% (91/94)	98% (90/92)
<i>Klebsiella pneumoniae</i>	95% (20/21)	83% (19/23)
<i>Enterococcus faecalis</i>	100% (17/17)	67% (14/21)
<i>Proteus mirabilis</i>	92% (11/12)	100% (10/10)
<i>Enterobacter aerogenes</i>	100% (4/4)	100% (6/6)
<i>Pseudomonas aeruginosa</i>	100% (3/3)	100% (3/3)

The clinical success rate in CIPRO XR treated patients with a diagnosis of complicated urinary tract infection was 96.4% (159/165) compared to 93.1% (161/173) in patients treated with immediate-release ciprofloxacin. The bacteriological eradication rates at the test-of-cure visit for the microbiologically evaluable patients with a diagnosis of acute

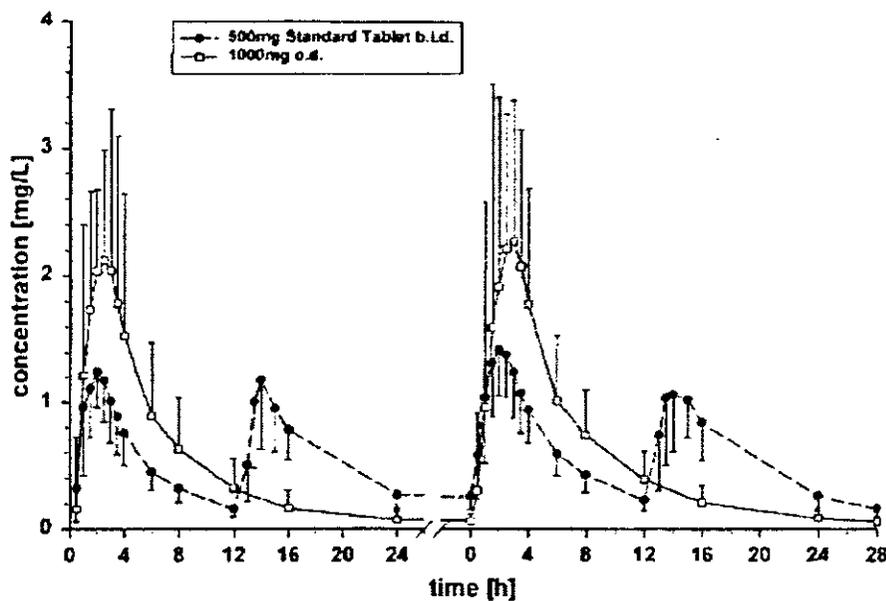
uncomplicated pyelonephritis caused by *Escherichia coli* was 97.2% (35/36) compared to 100.0% (41/41) in patients treated with immediate-release ciprofloxacin. Please refer to the medical officer's review for a more detailed discussion of safety and efficacy issues.

**Do PK parameters change with time following chronic dosing?**

The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new 1000 mg XR formulation to healthy male subjects resulted in comparable pharmacokinetic parameters suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation.

The peak to trough (PTF) ratios were 4.02 for the CIPRO<sup>®</sup> XR formulation and was 2.65 for the IR formulation. The presence of an IR component in the CIPRO<sup>®</sup> XR product may be the cause for higher ratio.

**Figure 11.5.2-1:** Plasma concentration vs time curves for ciprofloxacin (BAY q 3939) including the geometric standard deviation in study 10324 (N=18)



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

The plasma and urine drug concentration measurements were not obtained in patients and hence a comparison of the PK of healthy volunteers to patients cannot be made.

### What are the basic PK parameters?

The PK parameters in healthy volunteers are given below:

Table 2-2 Ciprofloxacin steady state pharmacokinetics (Mean  $\pm$  SD) following multiple (5 days) oral dose administration of Cipro<sup>®</sup> XR 1g once daily and conventional Cipro<sup>®</sup> 0.5g twice daily in healthy male subjects

Study	N	C <sub>max</sub> (mg/L)	AUC (mg <sup>2</sup> h/L)	T <sub>1/2</sub> (hr)	T <sub>max</sub> (hr) <sup>a</sup>	
CIPRO XR 1g QD	10324	18	3.11 $\pm$ 1.08	16.83 $\pm$ 5.65	6.31 +0.72	2.0 (1-4)
CIPRO 0.5g BID			2.06 $\pm$ 0.41	17.04 $\pm$ 4.79	5.86 +0.89	2.0 (0.5-3.5)

<sup>a</sup>median (range)

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

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

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

#### a) Elderly

Pharmacokinetic studies of immediate-release Cipro Tablets (single dose) and intravenous ciprofloxacin (single and multiple dose) indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) compared to young adults. C<sub>max</sub> is increased by 16% to 40%, and mean AUC is increased by approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant and no dosage adjustments for age alone (i.e., without renal impairment) is needed.

#### b) Pediatric patients

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

#### c) Gender

No studies were conducted to study the effect of gender on the pharmacokinetics of CIPRO XR 1000 mg product.

#### d) Race

No studies were conducted to study the effect of race on the pharmacokinetics of CIPRO XR 1000 mg product.

**e) Renal impairment**

The applicant's proposal to reduce the dosage of CIPRO XR 1000 mg in patients with severe renal impairment to CIPRO XR 500 mg is acceptable. For patients with mild and moderate renal impairment, no dosage adjustments are recommended. As a Phase IV commitment, the applicant has been asked to perform additional Monte-Carlo simulations to characterize the exposure of CIPRO XR 1000 mg (administered QD for 14 days) in patients with mild and moderate renal impairment. Based on these results, changes in labeling may be recommended at a later time.

**f) Hepatic impairment**

No significant changes in the pharmacokinetics of ciprofloxacin have been observed in studies of patients with stable chronic cirrhosis of the liver. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. There is no difference in the proposed labeling for CIPRO<sup>®</sup> 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<sup>®</sup> XR group and 4 in the Cipro 250 mg BID). Four of the pregnancies resulted in spontaneous abortions (2 in each group). L

1 One patient in the Cipro 250 mg BID gave birth to a full-term infant via normal vaginal delivery during the study period. There were neither maternal complications nor infant abnormalities. The infant's Apgar score at 1 and 5 minutes was 8 and 9, respectively.

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

The effect of aluminium and magnesium containing antacid and proton pump inhibitor, omeprazole, on the exposure of Cipro XR 1000 mg was previously evaluated during the review of Cipro XR 500 mg product. For details please refer to the biopharm review of the Cipro XR 500 mg product (NDA 21-473) by Dakshina Chilukuri. The recommendations for dosage adjustments of antacids and omeprazole are given below:

**Maalox:**

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

**Omeprazole:**

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

**What is the effect of food on the bioavailability (BA) of CIPRO XR?**

The effects of food on the pharmacokinetics of ciprofloxacin following administration of a single dose of the 1000 mg XR formulation was investigated in a two-way crossover study. Subjects received study drug either after an overnight fast or a standard high-fat breakfast. As shown in the table below, ciprofloxacin pharmacokinetics are not altered by co-administration with food. The 90% CI for C<sub>max</sub> and AUC demonstrated bioequivalence between fed and fasted conditions.

**PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles**

PK parameter*	1000 mg XR fasted (N=20)	1000 mg XR fed (N=20)
C <sub>max</sub> (mg/mL)	2.83 (1.35)	3.12 (1.16)
AUC <sub>0-24</sub> (mg-h/mL)	15.2 (1.35)	15.8 (1.19)
AUC <sub>inf</sub> (mg-h/mL)	15.9 (1.36)	16.6 (1.21)
T <sub>max</sub> (h) <sup>#</sup>	2 (0.5-3.5)	3.5 (2-4.0)
T <sub>1/2</sub> (h)	5.76 (1.13)	5.74 (1.12)

\*Parameters are presented as geometric means (geometric SD)

<sup>#</sup>Values are medians for t<sub>max</sub>

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

CIPRO<sup>®</sup> XR can be administered without regard to meals.

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

Following are the proposed dissolution testing conditions and acceptance criteria

Apparatus:	USP Apparatus II (Paddle)
Dissolution medium:	900 mL 0.1N HCl
Bath temperature:	37 ± 0.5 °C
Rotation speed:	50 rpm
Acceptance Criteria:	30 minutes: $\geq 10\%$
	60 minutes: $\geq 25\%$
	120 minutes: NLT $\geq 35\%$

Based on the data provided by the applicant (see below), the proposed method and acceptance criteria are acceptable. The typical dissolution profile of ciprofloxacin 1000 mg tablets is given below:

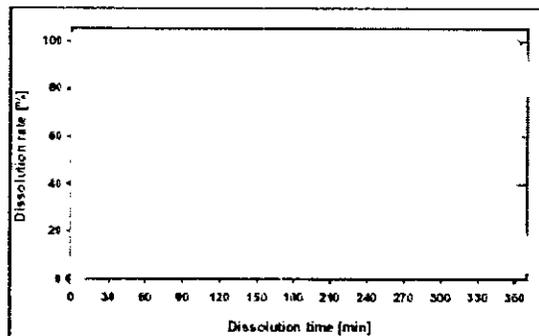


Fig. 1: Typical dissolution profile of Cipro MR Tablets 1 G  
(USP paddle apparatus, 50 rpm, 0.1N HCl, 900 ml)

The influence of the pH of the dissolution medium upon the dissolution characteristics of ciprofloxacin 1000 mg tablets was studied. The dissolution data at each pH is given below:

Ciprofloxacin MR Tabl 1G Coat 765, batch no 529234D (K-V.8), dissolution medium: 0.1N HCl

sampling time	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Average [%]	COV [%]
15 [min]													25	27.2
30													44	12.0
45													56	7.6
60													65	6.2
90													77	5.9
120													86	5.4
180													96	3.5
240													99	2.5
300													99	2.6
360													100	2.6

Ciprofloxacin MR Tabl 1G Coat 765, batch no 529234D (ME: S-X.2) diss: 0.01N HCl + NaCl

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average [%]	COV [%]
15 [min]							34	14.0
30							48	5.3
45							58	5.2
60							67	5.8
90							80	5.8
120							89	4.4
180							98	1.8
240							101	2.2
300							101	2.2
360							101	2.3

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Ciprofloxacin MR Tabl 1G Coat 765, batch no 529234D (ME S-IX 2), diss. medium: acetate buffer pH 4.5

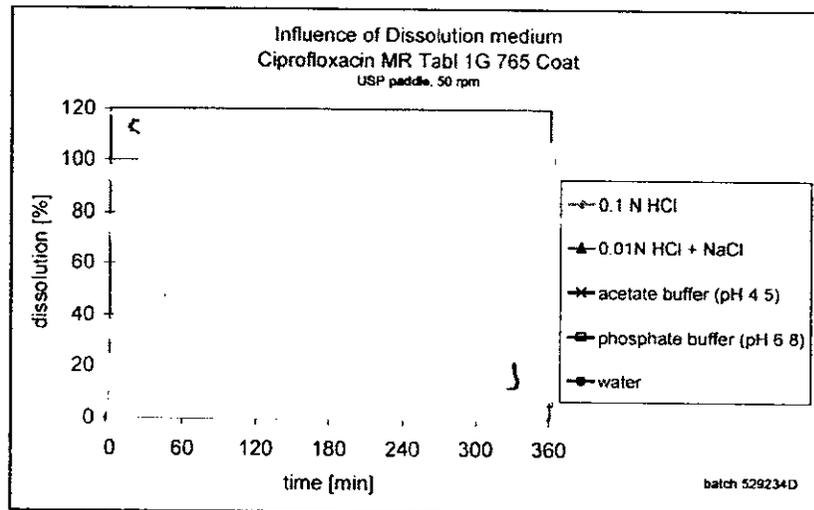
sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average [%]	COV [%]
15 [min]							27	24.9
30							44	21.3
45							56	16.1
60							65	13.1
90							78	10.5
120							88	8.5
180							98	4.8
240							101	1.9
300							101	1.6
360							101	1.6

Ciprofloxacin MR Tabl 1G Coat 765, batch no 529234D (ME S-VIII 16), dissolution medium: water

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average [%]	COV [%]
15 [min]							21	19.5
30							39	19.1
45							51	15.2
60							60	11.5
90							74	7.9
120							84	5.2
180							95	2.8
240							100	1.3
300							101	1.0
360							100	1.2

Ciprofloxacin MR Tabl 1G Coat 765, batch no 529234D (ME S-IX 6) diss. medium: phosphate buffer pH 6.8

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average [%]	COV [%]
15 [min]							1	11.7
30							2	6.2
45							3	4.5
60							3	3.8
90							4	3.1
120							4	3.0
180							5	3.1
240							6	3.3
300							6	3.8
360							7	3.9



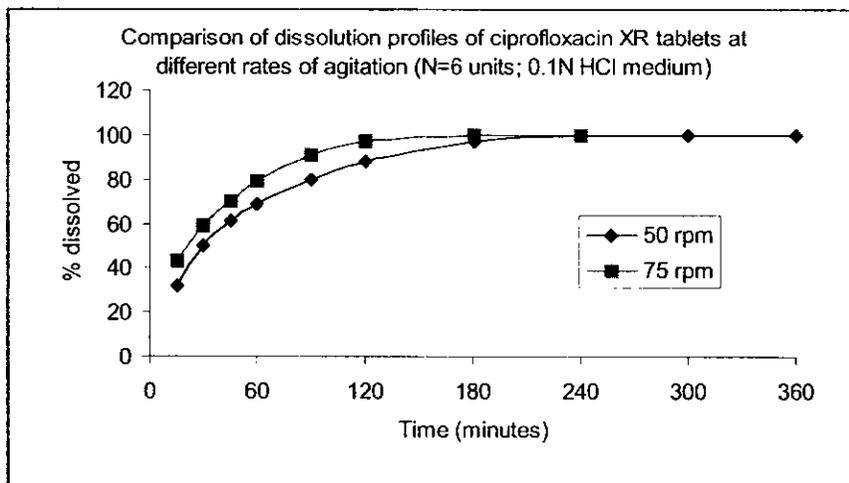
The influence of the agitation rate upon the dissolution characteristics of ciprofloxacin 1000 mg tablets was studied.

Ciprofloxacin MR Tabl IG Coat 760, batch no 528480 E (K-V 1) diss. medium: 0.1N HCl, 50 rpm

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average [%]	COV [%]
15 [min]							32	18.7
30							50	4.1
45							61	2.0
60							69	2.3
90							80	2.5
120							88	1.9
180							97	1.4
240							100	2.1
300							100	2.1
360							100	2.2

Ciprofloxacin MR Tabl IG Coat 760, batch no 528480 E (ME S-VIII.2) diss. medium: 0.1N HCl, 75 rpm

sampling time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average [%]	COV [%]
15 [min]							43	12.1
30							59	4.9
45							70	4.2
60							79	3.8
90							91	3.0
120							97	2.1
180							100	0.8
240							100	0.8



**How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

The following assays were validated and used to determine ciprofloxacin concentrations in plasma and urine. A review of the analytical methodologies is presented below:

**HPLC conditions of the assay in plasma samples:**

Instrument: [ ]

] ]

[ ]

] ]

Internal Standard: Ofloxacin

Linearity: [ ] mg/L

QC samples: [ ] ]

Limit of Quantitation: — mg/L

Specificity and Accuracy: The [ ] ] procedures allowed a good separation of the components of interest from endogenous compounds.

A validation series [ ] ] yielded the following precision and accuracy data for ciprofloxacin:

Concentration [mg/L]	[ ]				] ]
Accuracy (n=18) [%]	[ ]				] ]
Precision (n=18) [%]	[ ]				] ]

**HPLC conditions of the assay in urine samples:**

**Instrument:** [ ]

] ]

Internal Standard: Ofloxacin

Linearity: [ ] mg/L

QC samples: [ ] mg/L

Limit of Quantitation: — mg/L.

Specificity and Accuracy: The [ ] procedures allowed a good separation of the components of interest from endogenous compounds.

A validation series [ ] yielded the following precision and accuracy data for ciprofloxacin:

Concentration [mg/L]	[ ]		
Accuracy (n=6) [%]	[ ]		
Precision (n=6) [%]	[ ]		

## APPENDICES

1. Proposed labeling with Clinical Pharmacology Reviewer Comments
2. Clinical Pharmacology/Biopharmaceutics Individual Study Reviews
3. Review of the Monte-Carlo Simulation Report

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

## Appendix-2: Clinical Pharmacology/Biopharmaceutics Individual Study Reviews

1. **Report 10324:** Open, Randomized, Non-Controlled, Multiple Dose, Twofold Cross-Over Study to Assess the Single Dose and Steady State Pharmacokinetics of the Oral Ciprofloxacin 1000mg Once Daily Tablet During a Five Days Treatment in Comparison to the BID Treatment with the 500mg Immediate Release Tablet in Healthy Male Subjects.

**Objectives:** Primary objective was to evaluate the single dose and steady state pharmacokinetics of an oral 1000 mg ciprofloxacin once daily tablet (CIPRO XR) given to healthy subjects after an overnight fast according to a once daily dosing regimen for five days. In addition a comparison to the standard immediate treatment regimen (500 mg immediate release given bid) was performed.

**Investigator:** [ ]

### Formulations:

1. Ciprofloxacin Tablet Lack, 500 mg, batch number 5228631
2. Ciprofloxacin 1000 mg XR tablets, batch number 528480E

**Subjects:** 19 healthy subjects between 18 and 55 years were selected.

**Study design:** This was a single center, open label, randomized, non-controlled, multiple dose study in 19 healthy subjects and the treatment regimen was as follows:

- A: 1000 mg Ciprofloxacin once daily tablet formulation given once a day over a period of 5 days.
- B: 500 mg Ciprofloxacin standard tablet formulation (IR) tablet given bid over a period of 5 days.

The treatments were administered with a washout period of one week.

**Sampling:** For Treatment A, on day 0 and on day 4, 3 mL blood samples were collected in [ ] at 0, 0.5, 1.0, 2.0, 3, 3.5, 4, 6, 8, 12, 16 and 24 h following drug administration. For Treatment B, the sampling schedule was at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 6, 8, 12, 13, 13.5, 14, 15, 16 and 24 h following drug administration. The samples were centrifuged for 5 min at room temperature and [ ] g within 4 hours after collection. Plasma samples were stored at  $-20^{\circ}\text{C}$  until analysis was performed.

The total and fractional volume of urine was collected on the profile days during the following intervals: 0-4, 4-8, 8-12 and 24-28 h. Aliquots of 9 mL each were provided from each interval from the spontaneous urine before first administration.

**Assay:** Ciprofloxacin was determined in all available plasma and urine samples using a [ ] method with [ ] The internal standard used was Ofloxacin. The lower limit of quantitation was [ ] mg/L in plasma samples and [ ] mg/L in urine samples. The accuracy and precision of the assay

were 1% and 1%. The accuracy and precision of the urine assay were 1%.

**Pharmacokinetic Analysis:** The pharmacokinetic analysis was performed by the noncompartmental method using [ ]. The maximum plasma concentration ( $C_{max}$ ), maximum plasma concentration ( $C_{max ss}$ ) at steady state, time to maximum plasma concentration ( $T_{max}$ ), terminal elimination half-life ( $t_{1/2}$ ), 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 ( $Ae_{ur}$ )

**Statistical Analysis:** Exploratory statistical analyses by means of ANOVA were performed for the primary pharmacokinetic parameters of AUC,  $AUC_{0-24}$ ,  $C_{max}$ ,  $AUC_{0-24ss}$  and  $C_{max ss}$  of ciprofloxacin in order to compare the pharmacokinetics of the once daily formulation and the standard tablet.

**Results:**

The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized in Table 1. Also presented are the 90% confidence intervals for the test/reference ratios.

**Table 1. PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles**

PK parameter*	Treatment A: XR tablet given once-daily	Treatment B: IR tablet given bid	Mean Ratio of XR tablet/IR tablet	90% CI
$C_{max}$ (mg/mL)	2.53 (1.47)	1.94 (1.25)	1.34	1.20-1.49
$AUC_{0-24}$ (mg-h/mL)	14.1 (1.50)	14.5 (1.30)	0.99	0.89-1.09
$AUC_{ur}$ (mg-h/mL)	14.7 (1.52)	16.3 (1.34)	0.89	0.80-0.99
$AUC_{0-24 ss}$ (mg- h/mL)	16.0 (1.38)	16.5 (1.31)	0.98	0.91-1.05
$C_{max ss}$	2.95 (1.40)	2.02 (1.22)	1.47	1.31-1.66
$T_{max}$ (h) <sup>#</sup>	2.0 (1.0-3.5)	1.25 (0.5-3)	NC	NC
$T_{1/2}$ (h)	5.80 (1.12)	4.88 (1.17)	NC	NC
$Ae_{ur}$ 0-24 (mg)	354 (99.9)	329 (74.8)	NC	NC

\*Parameters are presented as geometric means (geometric SD) #Values are medians for  $t_{max}$  NC: Not Calculated

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Figure 11.5.2-1: Plasma concentration vs time curves for ciprofloxacin (BAY q 3939) including the geometric standard deviation in study 10324 (N=18)

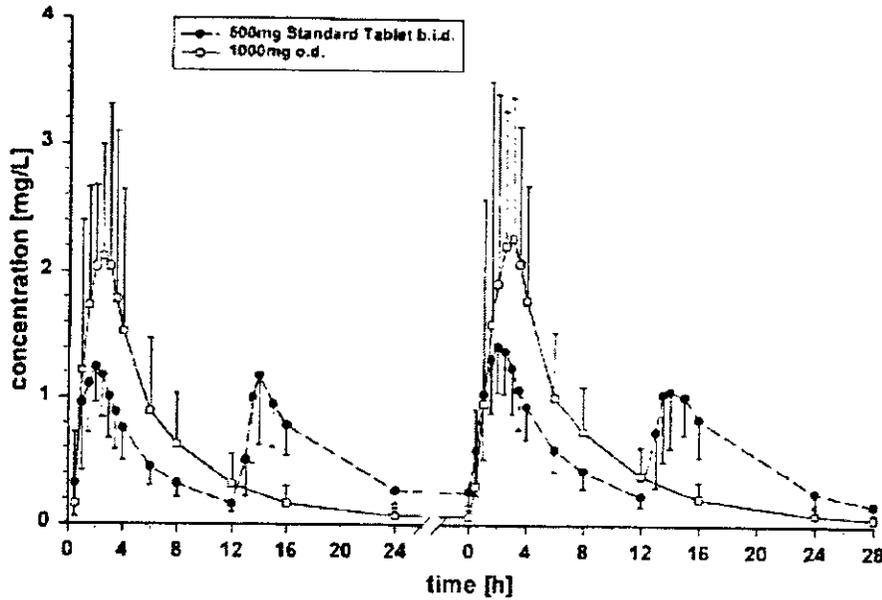
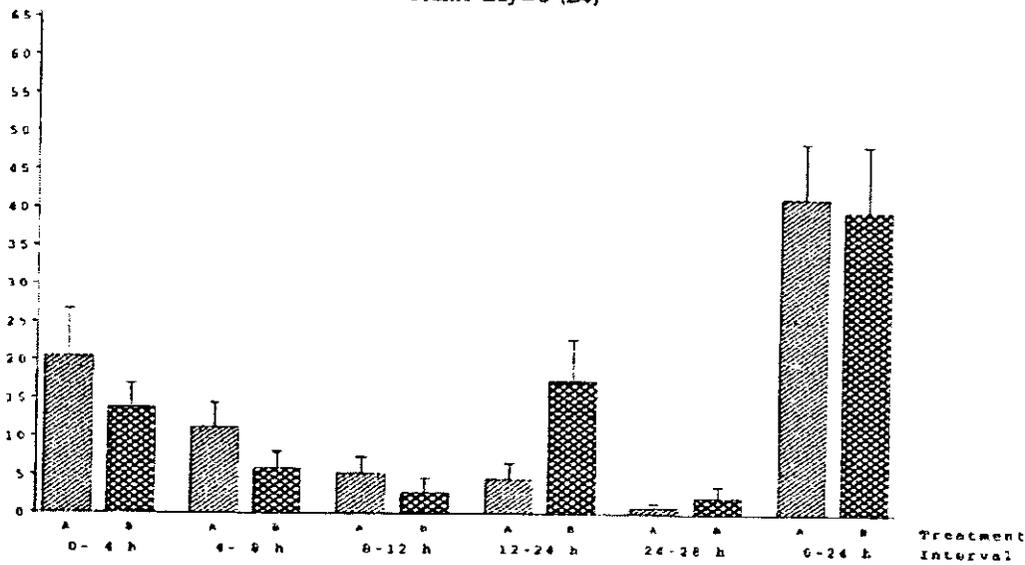


Figure 14.4-1.2  
 Mean Bar Chart for BAY Q 3939 Amount Excreted Into Urine (%)  
 All subjects valid for PK and safety (N=18)  
 Profile Day=5 (D4)



Treatment Key: A - 1000 mg BAY q 3939 od, B - 500 mg BAY q 3939 bid

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The  $AUC_{inf}$  of the 1000 mg ciprofloxacin once daily formulation was slightly lower (11%) than the bid treatment with the IR tablet. However, the 90% confidence intervals were within the 80-125% bioequivalence range.

The  $C_{max}$  of the 1000 mg ciprofloxacin once daily formulation was 34% higher than after the 500 mg bid treatment with the IR tablet. Also  $C_{max_{ss}}$  was increased by 47% comparing the 1000 mg XR tablet with the 500 mg bid tablet. This higher  $C_{max}$  following administration of the XR formulation may be due to the immediate release (IR) component in the XR formulation.

As seen in the above table, AUC and  $C_{max}$  were essentially not different between steady state and single dose suggesting linear pharmacokinetics and absence of significant accumulation.

As seen in Table 1 and in the Figure 2, the amount of ciprofloxacin excreted unchanged in urine ( $Ae_{ur}$ ) was comparable for the XR formulation and the IR formulation. In the urine, higher ciprofloxacin concentrations were reached for the XR formulation in the period until 12 hours post dosing compared to the IR tablet.

#### **Summary and Conclusions:**

The pharmacokinetics of ciprofloxacin after single and multiple once daily dosing (over 5 days) of a new XR formulation to healthy male subjects resulted in comparable extent of exposure pharmacokinetic parameters (AUC,  $Ae_{ur}$ ) suggesting absence of time and dose dependent pharmacokinetics and absence of clinically relevant accumulation. Peak exposure ( $C_{max}$ ) was approximately 30-40% higher with the XR formulation than with the immediate-release formulation.

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2. Study 10339: Not blind, randomized, triple cross-over, non-controlled study to compare the safety, tolerability and pharmacokinetics of two oral ciprofloxacin 1000 mg once daily tablet formulations administered as a single dose in the fed state and two doses of the 500 mg standard tablet given 12 h apart after an overnight fast to healthy male subjects.

**Objectives:** Primary objective was to compare the safety, tolerability and pharmacokinetics of two oral 1000 mg ciprofloxacin once daily formulations given after a continental breakfast with the marketed ciprofloxacin product given orally according to a bid dosing schedule as two doses of 500 mg to healthy subjects who fasted overnight.

**Investigator:** [redacted]

**Formulations:**

- Ciprofloxacin Tablet 500 mg, batch number 522863L
- Ciprofloxacin 1000 mg XR tablets, batch number 528480E (Formulation E760)
- Ciprofloxacin 1000 mg XR tablets, batch number 528613A (Formulation E780)

**Subjects:** 12 healthy subjects between 18 and 55 years were selected.

**Study design:** This was a single center, open-label, randomized, non-controlled study in 12 healthy male subjects and the treatment regimen was a single dose treatment with two 1000 mg Ciprofloxacin once daily tablet formulation (XR) given 15 minutes at the end of a continental breakfast (4 slices toast, 20g butter, 50g jam, 20g cheese, 200mL decaffeinated coffee, 3g sugar) and bid treatment with two 500 mg doses of the marketed standard tablet (IR, first dose given after an overnight fast).

The treatments were administered with a washout period of one week.

**Sampling:** For 1000 mg single dose administration, 3 mL blood samples were collected in [redacted] at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 16 and 24 h following drug administration. For 500 mg bid treatment with standard tablet, the sampling schedule was at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 13, 13.5, 14, 14.5, 15, 15.5, 16, 20, 24 and 30 h following drug administration. The samples were centrifuged for 5 min at room temperature and [redacted] g within 4 hours after collection. Plasma samples were stored at -20° C until analysis was performed.

**Assay:** Ciprofloxacin was determined in all available plasma samples using [redacted] method with [redacted]. The internal standard used was Ofloxacin. The lower limit of quantitation was [redacted] mg/mL in plasma and [redacted] mg/mL in urine. The accuracy and precision of the plasma assay were [redacted] and [redacted]%. The accuracy and precision of the urine assay were [redacted] and [redacted]%.

**Pharmacokinetic Analysis:** The pharmacokinetic analysis was performed by the noncompartmental method using [redacted]. The maximum

plasma concentration ( $C_{max}$ ), 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 and area under the plasma concentration curve versus infinite time ( $AUC_{inf}$ ).

**Statistical Analysis:** Exploratory statistical analyses by means of ANOVA were performed for the primary pharmacokinetic parameters of AUC,  $AUC_{0-24}$  and  $C_{max}$  of ciprofloxacin in order to compare the pharmacokinetics of the once daily formulation and the standard tablet.

**Results:**

The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized in Table 3. Also presented are the 90% confidence intervals for the test/reference ratios.

**Table 2. PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles**

PK parameter*	500 mg bid fasted	1000 mg XR (E760) fed (N=12)	1000 mg XR (E780) fed (N=12)
$C_{max}$ (mg/mL)	1.56 (1.38)	2.95 (1.30)	2.56 (1.24)
$AUC_{0-24}$ (mg-h/mL)	13.4 (1.37)	14.2 (1.22)	13.5 (1.28)
$AUC_{inf}$ (mg-h/mL)	15.4 (1.34)	14.8 (1.23)	14.0 (1.29)
$T_{max}$ (h) <sup>#</sup>	1.75 (0.5-2.53)	3.0 (1.5-4.0)	3.0 (1.5-4.0)
$T_{1/2}$ (h)	5.20 (1.18)	5.21 (1.14)	4.94 (1.09)

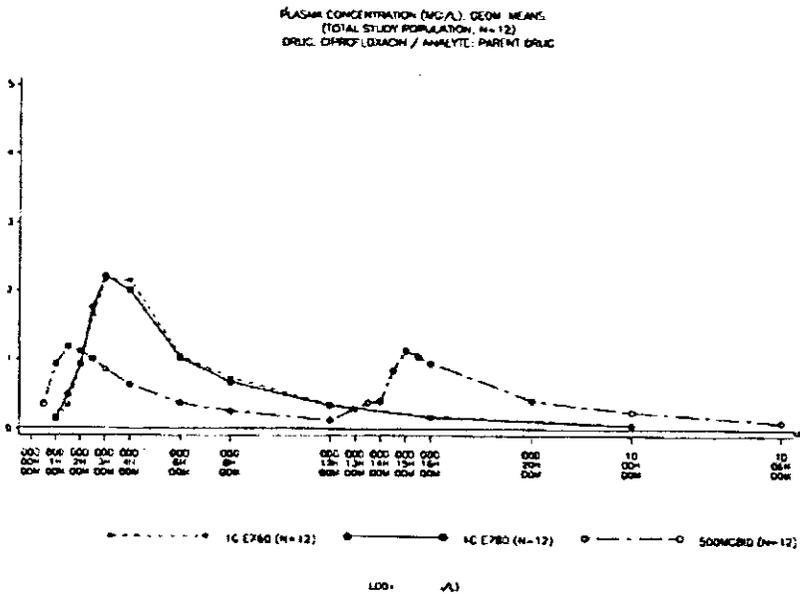
\*Parameters are presented as geometric means (geometric SD)

<sup>#</sup>Values are medians for  $t_{max}$

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Table 11.5.4-1: Point estimators (LS-means) and (exploratory) two-sided 90% confidence intervals for the ratios '1000 mg OD (E760) fed / 500 mg bid fasted' and '1000 mg OD (E780) fed / 500 mg bid fasted' with regard to the primary pharmacokinetic parameters AUC, AUC<sub>0-24</sub> and C<sub>max</sub> of ciprofloxacin (all subjects valid for PK, N=12)

Ratio	Parameter	N	estimated ratio (%)	90% confidence interval
1000 mg OD (E760) fed / 500 mg bid fasted	AUC	12	95.55	[87.95 ; 103.79]
	AUC <sub>0-24</sub>	12	105.85	[96.76 ; 116.02]
	C <sub>max</sub>	12	189.31	[169.19 ; 211.83]
1000 mg OD (E780) fed / 500 mg bid fasted	AUC	12	90.59	[83.39 ; 98.41]
	AUC <sub>0-24</sub>	12	100.69	[92.13 ; 110.48]
	C <sub>max</sub>	12	164.14	[146.69 ; 183.66]



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FIGURE 14.4 - 7.1  
 MEAN (± SD) (N) (URINE) - MEANS ± SD  
 (TOTAL STUDY POPULATION, N=12)  
 DRUG: CIPROFLOXACIN / ANALYTE: PARENT DRUG



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As shown in Table 3, the point estimators suggest that the oral bioavailability ( $AUC_{inf}$ ) of ciprofloxacin was 96% and 91% after the 1000 mg XR formulations E760 and E780 when compared to the 500 mg bid reference treatment. The 90% confidence intervals met the bioequivalence acceptance range of 80-125%.

As seen in the above Figure (14.4-7.1), the amount of ciprofloxacin excreted unchanged in urine ( $Ae_{ur}$ ) was comparable for the XR and IR formulations.

**Summary and Conclusions:**

After single dose administration of 1000 mg ciprofloxacin as XR tablet formulations E760 and E780 under fed conditions compared to the 500 mg IR standard tablet bid under fasted condition the relative bioavailability of ciprofloxacin was 96% and 91%, respectively.

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3. **Report 10321: Not-blind, randomized, single dose, two-fold crossover, non-controlled study to evaluate the effect of a high calorie, high fat meal on the pharmacokinetics of a ciprofloxacin 1000 mg XR formulation in healthy male subjects.**

**Objectives:** The primary objective of the study was to evaluate the effect of a high calorie, high fat meal on the pharmacokinetics of a new oral Ciprofloxacin 1000 mg XR formulation given to healthy subjects who fasted overnight.

**Investigator:** [ ]

**Formulations:**

Ciprofloxacin Tablet, 500 mg, batch number 528481C

**Subjects:** 20 healthy subjects between 18 and 55 years were selected.

**Study design:** This was a single center, open-label, randomized, non-blinded, two-way crossover non-controlled study in 20 healthy male subjects; single dose treatment with the 500 mg Cipro XR formulation given on two occasions:

- Administered after an overnight fast with 180 mL non-sparkling water.
- Administered 5 minutes after the end of a high calorie, high fat meal, eaten within 30 minutes after a 10 hour fast, with 180 mL of non-sparkling water.

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

**Sampling:** 3 mL blood samples were collected in [ ] at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 6, 8, 12, 15 and 24 h following drug administration. The samples were centrifuged for 5 min at room temperature and [ ] g within 4 hours after collection. Plasma samples were stored at -20° C until analysis was performed.

**Assay:** Ciprofloxacin was determined in all available plasma samples using [ ] method with [ ] The internal standard used was Ofloxacin. The lower limit of quantitation in plasma and urine were [ ] mg/mL, respectively. The accuracy and precision of the plasma assay were [ ] %. The accuracy and precision of the urine assay were [ ] %.

**Pharmacokinetic Analysis:** The pharmacokinetic analysis was performed by the noncompartmental method using [ ] The maximum plasma concentration ( $C_{max}$ ), 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 and area under the plasma concentration curve versus infinite time ( $AUC_{inf}$ ).

**Statistical Analysis:** Exploratory statistical analyses by means of ANOVA were performed for the primary pharmacokinetic parameters of AUC,  $AUC_{0-24}$  and  $C_{max}$  of

ciprofloxacin in order to compare the pharmacokinetics of the once daily formulation and the standard tablet.

**Results:**

The pharmacokinetic parameters derived from the individual ciprofloxacin plasma profiles are summarized in Table 6. Also presented are the 90% confidence intervals for the test/reference ratios.

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**Table 3. PK parameters of ciprofloxacin derived from the individual ciprofloxacin plasma profiles**

PK parameter*	1000 mg XR fasted (N=20)	1000 mg XR fed (N=20)
C <sub>max</sub> (mg/mL)	2.83 (1.35)	3.12 (1.16)
AUC <sub>0-24</sub> (mg-h/mL)	15.2 (1.35)	15.8 (1.19)
AUC <sub>inf</sub> (mg-h/mL)	15.9 (1.36)	16.6 (1.21)
T <sub>max</sub> (h) <sup>#</sup>	2 (0.5-3.5)	3.5 (2-4.0)
T <sub>1/2</sub> (h)	5.76 (1.13)	5.74 (1.12)

\*Parameters are presented as geometric means (geometric SD)

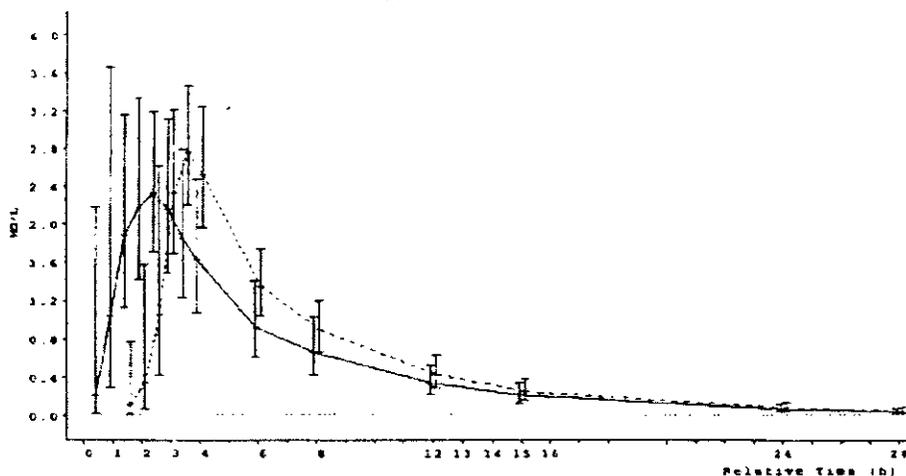
<sup>#</sup>Values are medians for t<sub>max</sub>

**Table 11.5 4-1. Mean ratios and 90% confidence intervals for primary parameters C<sub>max</sub>, AUC, and AUC<sub>0-24</sub> of ciprofloxacin**

Parameter	Mean ratio Fed/Fasted	90% confidence interval	Within-Subject CV (%)
C <sub>max</sub>	1.098	(0.996, 1.210)	17.32
AUC	1.042	(0.945, 1.148)	17.36
AUC <sub>0-24</sub>	1.035	(0.939, 1.142)	17.44

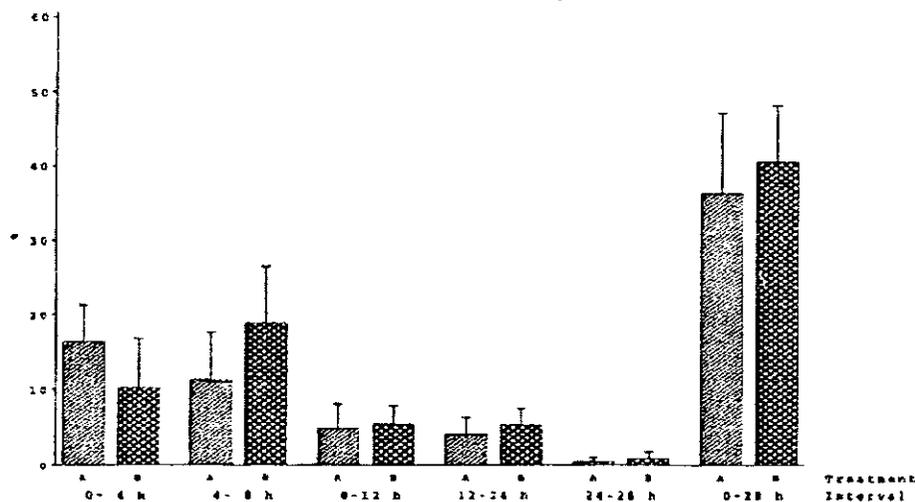
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Geometric Mean Time Courses of BAY Q 3939 Plasma Concentrations (MG/L), including 1 SD range  
 All subjects valid for PK and safety (N=19)  
 linear scale



Note. Solid line = 1000 mg BAY q 3939 in fasted state, dashed line = 1000 mg BAY q 3939 in fed state  
 Values below LOQ (— µg/l) were replaced by half of LOQ in calculations if at least 2/3 of the data were above LOQ.

Figure 14.4-12  
 Mean Bar Chart for BAY Q 3939 Amount Excreted Into Urine (%)  
 All subjects valid for PK and safety (N=19)



Treatment Key: A - 1000 mg BAY q 3939 in fasted state, B - 1000 mg BAY q 3939 in fed state

As shown in Table 6, the 90% CI for the mean ratios were completely within the required bioequivalence ranges for AUC, AUC<sub>0-24</sub> and C<sub>max</sub>, respectively. Thus, the 500 mg XR ciprofloxacin in the fasting and fed states are bioequivalent. The T<sub>max</sub> was prolonged from 2 hr to 3.5 hours following administration of the XR tablet with food.

As seen in the above Figure (14.4-1.2), the amount of ciprofloxacin excreted unchanged in urine (Ae<sub>ur</sub>) was comparable for the XR formulations under fed and fasted conditions.

**Summary and Conclusions:**

Based on the above results, it may be concluded that with respect to  $AUC_{0-24}$ ,  $AUC_{inf}$  and  $C_{max}$ , a clinically relevant food effect is absent.

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### Appendix-3: Review of the Monte-Carlo Simulation Report

**Report No.: PH-32741: A new modified release Ciprofloxacin XR<sup>®</sup> tablet:  
Pharmacokinetic simulations of different dosing regimens in renally impaired  
patients compared to the standard Cipro<sup>®</sup> IR tablet**

#### **Objectives:**

To establish a pharmacokinetic model of ciprofloxacin from Phase studies in healthy volunteers after oral administration of Cipro IR and Ciprofloxacin XR for 5 days bid and qd, respectively.

To compare the effect of renal impairment on the single dose and steady state pharmacokinetics of ciprofloxacin, when given orally in form of an immediate release standard tablet (Cipro<sup>®</sup>) and as a modified release tablet (Ciprofloxacin XR<sup>®</sup>) to healthy subjects by means of population pharmacokinetic simulations based on available Phase I studies.

The following Monte-Carlo simulations have been performed to estimate the influence of renal function on the plasma pharmacokinetics under different dosing regimens:

1. Pharmacokinetics of ciprofloxacin in patients with severe renal impairment ( $CL_{Cr} < 30 \text{ mL/min/1.73m}^2$ ) receiving 500 mg Ciprofloxacin XR<sup>®</sup> tablets once daily for three days
2. Pharmacokinetics of ciprofloxacin in patients with mild to moderate renal impairment ( $90 \text{ mL/min/1.73m}^2 > CL_{Cr} > 30 \text{ mL/min/1.73m}^2$ ) receiving 500 mg Cipro<sup>®</sup> tablets twice daily for three days
3. Pharmacokinetics of ciprofloxacin in patients with severe renal impairment ( $CL_{Cr} < 30 \text{ mL/min/1.73m}^2$ ) receiving 500 mg Cipro<sup>®</sup> tablets once daily or once every 18 hours for three days
4. Pharmacokinetics of ciprofloxacin in subjects with normal renal function receiving 750 mg Cipro<sup>®</sup> tablets twice daily for 14 days Monte Carlo simulations have been done by using nonlinear mixed

#### **Methodology:**

Monte Carlo simulations have been done by using nonlinear mixed effect modeling established within NONMEM V version 1.1. The model for the PK of ciprofloxacin as XR and IR tablet has been established with data from Phase I trials in healthy male volunteers (Study #PPK 02-006). The exposure parameters  $C_{max}$  and AUC were estimated by using SAS 8.2 and WinNonlin 4.0.1 (Pharsight Inc.). For each simulation scenario the plasma-concentration time profile of a typical subject has been simulated 100 times. From these profiles descriptive statistics were calculated.

#### **Assumptions:**

Since no experimental data are available in renally impaired patients for the Ciprofloxacin XR, the following assumptions were made:

1. The pharmacokinetic parameters  $V_c$ ,  $V_p$ ,  $Q$ ,  $K_a$  and lag time as well as their estimates of variability are assumed to be not affected by renal impairment. In addition, it was also assumed that the variability of  $CL/f$  of ciprofloxacin is not altered by renal impairment. Previous pharmacokinetic evaluation in renally impaired patients exhibited somewhat lower volume of distribution expressed as  $V_{ss}$  in severe renal impairment. However, other study data indicate that the volume of distribution expressed as  $V_z/f$  was not influenced by  $CL_{cr}$ . Consequently, the volume parameters estimated in the Phase I studies in healthy volunteers were assumed to be independent of renal function, which would be consistent with general pharmacokinetic knowledge. This assumption is supported by the results of the model validation in renally impaired subjects.
2. To describe the influence of renal impairment on the plasma pharmacokinetics of ciprofloxacin after oral administration of Ciprofloxacin XR, the linear relationship established previously after intravenous administration of ciprofloxacin to renally impaired patients between total body clearance and creatinine clearance can be transferred as follows into the model:  
 Ciprofloxacin XR\*:  $CL/f$  (L/h) =  $67.4 + 0.4156 * (CL_{cr} - 120)$  (mL/min/1.73 m<sup>2</sup>) - 67.4 L/h - 0.4156 (slope of  $CL=f(CL_{cr})$  after intravenous administration = 0.2909 slope corrected for bioavailability (F) in  $CL/f$  of ciprofloxacin (70 %)) - 120 mL/min/1.73 m<sup>2</sup>: Average  $CL_{cr}$  of healthy male Cipro\* IR:  $CL/f$  (L/h) =  $65.6 + 0.4156 * (CL_{cr} - 120)$  (mL/min/1.73 m<sup>2</sup>) - 65.6 L/h – Estimate of  $CL/f$  (PK model 190 – PK of Cipro\* IR, see Appendix)
3. Other covariates found during prior modeling (like weight influencing CL) were held constant, i.e. values assigned in a way that these covariates do not influence the simulation (Standard patient: body height = 180 cm, body weight = 80 kg, FAT=18 (they are set to the mean values in the data underlying the model)).
4. The bioavailability of ciprofloxacin is known to be not influenced by renal impairment. Therefore,  $f$  was setup independent of renal function as 70 % as determined in various studies.
5. The studies (IMPACT # 10324 and 10325) used for model development were performed in healthy male volunteers. Since no relevant gender influence on the pharmacokinetics of ciprofloxacin is currently known, the simulation using the population PK model from healthy male volunteers incorporating the linear relationship of CL with  $CL_{cr}$  from male and female patients is considered to be relevant for male and female subjects.

All evaluations as far as modeling and simulation were performed using NONMEM V level 1.1, S-Plus 3.1 and SAS 8.2

]

[ The pharmacokinetic parameter  $AUC_{(0-24)}$  was calculated using WinNonlin 4.0.1 (Pharsight Inc.) according to the lin/log trapezoidal rule. The exposure parameter  $C_{max}$  as well as the statistical evaluations such as geometric mean and geometric standard deviation was calculated within SAS.

**Results:**  
**Simulation results**

In the present study the influence of renal impairment on the pharmacokinetics of ciprofloxacin following oral administration of the standard tablet and the new Ciprofloxacin XR\* tablet formulation was evaluated by means of Monte Carlo simulations. The structural population pharmacokinetic model including subjects' covariates only for body weight (covariate for CL) and FAT (covariate for peripheral volume) was developed by nonlinear mixed effect modeling implemented in NONMEM. The influence of renal impairment, which decreases the renal clearance of ciprofloxacin as one major clearance pathway, was factored in by implementing the linear functional relationship between kidney function (i.e. creatinine clearance) and renal clearance derived from studies in patients with various degrees of renal impairment following intravenous administration [9]. Based on the resulting structural model plasma concentration vs. time profiles were simulated for 100 patients with both covariates (body weight and fat content) of a typical subject for the following four simulation scenarios :

Simulation Scenario	Dosing regimen	Simulation Results
1	500 mg Ciprofloxacin XR* qd for 3 days in patients with severe renal impairment	Table 10-8 Figure 10-8 Figure 10-9
2	500 mg Cipro* IR bid for 3 days in patients with mild to moderate renal impairment	Table 10-9 Figure 10-10 Figure 10-11
3a	500 mg Cipro* IR qd for 3 days in patients with severe renal impairment	Table 10-10 Figure 10-12 Figure 10-13
3b	500 mg Cipro* IR every 18 hours for 3 days in patients with severe renal impairment	Table 10-11 Figure 10-14 Figure 10-15
4	750 mg Cipro* IR bid for 14 days in patients with normal renal function	Table 10-12 Figure 10-16

For each scenario, peak concentrations and exposure ( $C_{max}$ , AUC,  $AUC_{(0-24)}$ ) were evaluated by descriptive univariate statistical methods. The results are summarized in Table 10-8 to Table 10-12 and Figure 10-8 to Figure 10-16 (including plots of individual profiles ("spaghetti plots")).

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### Exposure Comparison of the different Simulation Scenarios

**Table 10-1: Comparison of predicted C<sub>max</sub> [mg/L] for the different simulation scenarios [geo. mean/geom. sd (range)]**

Scenario	Dosing regimen	Simulation Results
1	500 mg Ciprofloxacin XR <sup>†</sup> qd for 3 days in patients with severe renal impairment	Day 1: 2.14/1.51 (0.58-5.74) Day 3: 2.49/1.43 (0.82-6.13)
2	500 mg Cipro <sup>†</sup> IR bid for 3 days in patients with mild to moderate renal impairment	Day 1: 2.55/1.56 (0.85-7.03) Day 3: 2.98/1.49 (1.02-7.03)
3a	500 mg Cipro <sup>*</sup> IR qd for 3 days in patients with severe renal impairment	Day 1: 2.49/1.61 (0.59-7.11) Day 3: 2.92/1.53 (1.13-8.01)
3b	500 mg Cipro <sup>*</sup> IR every 18 hours for 3 days in patients with severe renal impairment	Day 1: 2.99/1.58 (1.23-9.55) Day 3: 3.12/1.51 (1.32-9.5)
4	750 mg Cipro <sup>†</sup> IR bid for 14 days in patients with normal renal function	Day 1: 3.22/1.6 (0.64-9.27) Day 14: 3.63/1.58 (1.09-9.42)

**Figure 10-1: Comparison of predicted C<sub>max</sub> [mg/L] for simulation scenario 1-4**  
**Boxplots: Boxes show the median, 25 % and 75 % percentiles.**  
**Whiskers extend from the box to the most extreme value within 1.5 interquartile range. More extreme values are displayed with dots**

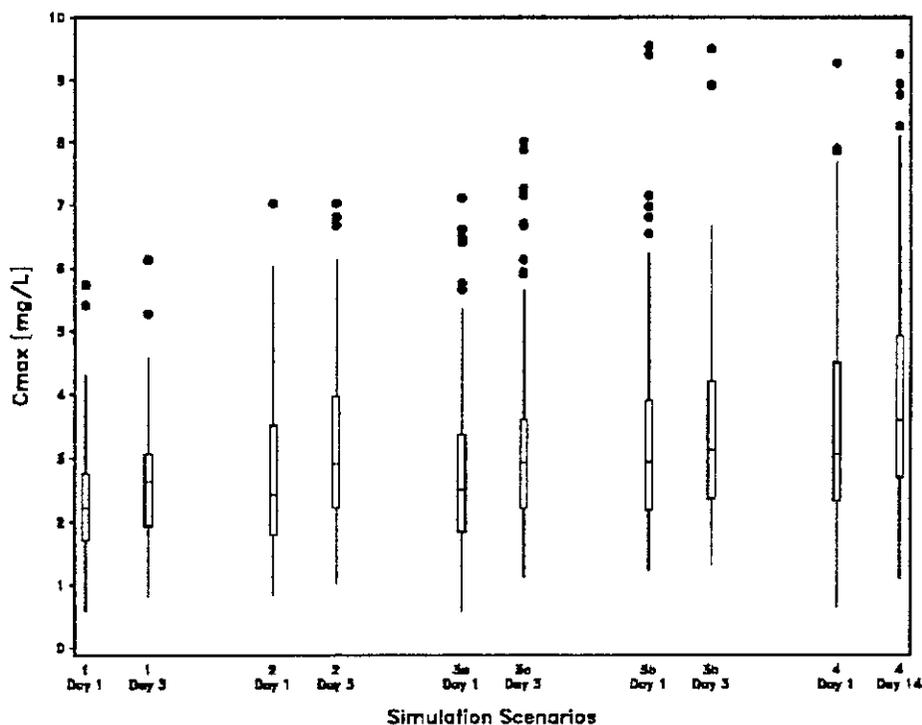
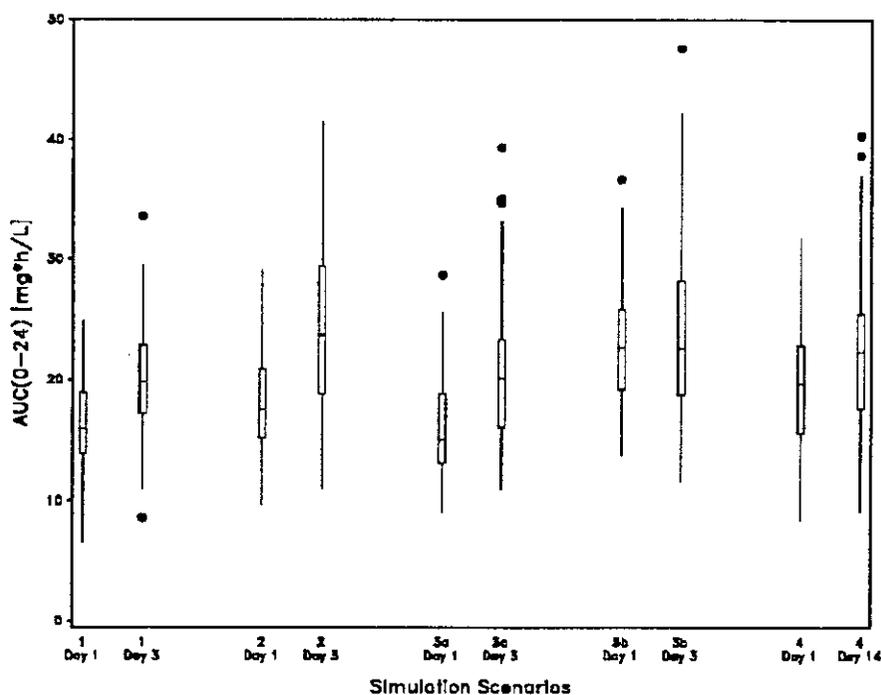


Table 10-2: Comparison of predicted AUC(0-24) [mg\*h/L] [geo. mean/geom. sd (range)]

Scenario	Dosing regimen	Simulation Results
1	500 mg CiproXR <sup>†</sup> qd for 3 days in patients with severe renal impairment	Day 1: 15.74/1.27 (6.51-24.86) Day 3: 19.49/1.27 (8.59-33.58)
2	500 mg Cipro <sup>†</sup> IR bid for 3 days in patients with mild to moderate renal impairment	Day 1: 17.47/1.27 (9.64-29.12) Day 3: 23.04/1.36 (10.92-41.52)
3a	500 mg Cipro <sup>†</sup> IR qd for 3 days in patients with severe renal impairment	Day 1: 15.47/1.29 (9-28.7) Day 3: 19.78/1.34 (10.97-39.36)
3b	500 mg Cipro <sup>†</sup> IR every 18 hours for 3 days in patients with severe renal impairment	Day 1: 22.15/1.26 (13.79-36.63) Day 3: 23.25/1.37 (11.61-47.63)
4	750 mg Cipro <sup>†</sup> IR bid for 14 days in patients with normal renal function	Day 1: 18.84/1.31 (8.33-31.78) Day 14: 21.6/1.34 (9.12-40.36)

Figure 10-2: Comparison of predicted AUC(0-24) [mg\*h/L] for simulation scenario 1-4

Bloxxplots: Boxes show the median, 25 % and 75 % percentiles. Whiskers extend from the box to the most extreme value within 1.5 interquartile range. More extreme values are displayed with dots.



The simulations predict that the highest drug concentrations are reached in subjects with healthy kidney function receiving a 750 mg bid IR dosing schedule (Scenario 4) or patients with severe renal impairment receiving a 500 mg IR dose every 18 hours (Scenario 3b). For scenario 1, variability of the  $C_{max}$  predictions was the lowest among all dosing regimen simulated. With respect to extent and variability of drug exposure scenario 1 (XR tablet, qd, severe renal impairment) and 3a (IR tablet, qd, severe renal impairment) were comparable as expected from the clinical pharmacokinetic properties of both formulations. Highest exposure data (extent and variability) were predicted for the scenario 3b (500 mg every 18 hours, severe renal impairment) with the extremes exceeding the predictions for the highest approved dosing regimen (750 mg bid, scenario 4), which is in accord with the pharmacokinetic properties of ciprofloxacin. The exposure data confirm the conclusions drawn from clinical study data for dose adjustments in patients with severe renal impairment.

#### **Overall Summary and Conclusion**

The simulations predict that the maximum approved dosing regimen of 750 mg bid for the treatment of severe infections in patients with normal kidney function covers peak concentrations and exposure resulting from application of 500 mg ciprofloxacin qd in form of the XR<sup>®</sup> tablet in patients with severe renal impairment.

#### **Reviewer Comments:**

1. It appears the applicant used First-Order (FO) method in the modeling and simulation. It is known that First Order Conditional Estimation (FOCE/INTERACTION) method is preferable for a relatively dense data set. Please address why only FO was used.
2. In the simulation, according to the code,  $CL_{cr}$  of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renal impaired and severe renal impaired, respectively. The approach is considered to be inadequate. It is preferable to simulate with continuous distribution of  $CL_{cr}$  ranges of normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment.
3. The applicant used the established relationship (published data) between clearance (CL) of ciprofloxacin and creatinine clearance ( $CL_{cr}$ ). However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of oral Cipro IR formulation and use it for the purpose of modeling and simulations. We recommend that the applicant re-develop the relationship between clearance (CL) and creatinine clearance ( $CL_{cr}$ ) and compare with the previous results.
4. Based on review of the Monte-Carlo simulations, the safety of CIPRO XR 500 mg administered QD to patients with uncomplicated UTI and severe renal impairment is acceptable. Also, based on principles of linear pharmacokinetics, extrapolation of the exposure can be made from the 3-day regimen in uncomplicated UTI to 14-day

regimen in complicated UTI and acute pyelonephritis. This means that the applicant's proposal to reduce the dosage from CIPRO XR 1000 mg to 500 mg for patients with complicated UTI and severe renal impairment is acceptable from a safety perspective.

5. The issue of dosage adjustment of CIPRO XR 1000 mg to patients with complicated UTI and acute pyelonephritis and mild to moderate renal impairment has not been addressed by the applicant in NDA 21-554. Specifically, it is unknown if the  $C_{max}$  and AUC following administration of CIPRO XR 1000 mg to patients with mild to moderate renal impairment would result in exposure causing higher incidence of adverse events. It is recommended that the applicant perform Monte-Carlo simulations to obtain exposure information following administration of CIPRO XR 1000 mg in patients with mild to moderate renal impairment.
6. Upon review of the safety data in Clinical Study 100275, the adverse events observed following administration of CIPRO XR 1000 mg to patients with normal renal function and to patients with mild to moderate renal impairment are similar. However, the exposure following administration of CIPRO XR 1000 mg to patients with mild to moderate renal impairment is likely to be higher than the exposure obtained after administration of 750 mg bid. But considering the overall safety profile of ciprofloxacin, it may be acceptable to administer a dose of CIPRO XR 1000 mg to patients with mild to moderate renal impairment suffering from complicated UTI. As a Phase IV commitment, the applicant should be asked to perform Monte-Carlo simulations to obtain the exposure of ciprofloxacin in mild to moderate renally impaired patients. Based on the information obtained from the simulations, changes in labeling recommendations may be made.

**Recommendations:**

1. It appears the applicant used FO method in the modeling and simulation. It is known that FOCE/INTERACTION method is preferable for a relatively dense data set. Please address why only FO was used.
2. In the simulation, according to the code,  $CL_{cr}$  of 120 mL/min, 60 mL/min and 20 mL/min were selected to represent healthy, moderate/mild renally impaired and severely renal impaired, respectively. This approach is considered to be inadequate. It is preferable to simulate with ranges of  $CL_{cr}$  values for normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment. Therefore, as a Phase IV commitment, please perform additional Monte-Carlo simulations to obtain estimates of ciprofloxacin systemic exposure after administration of the following regimens:
  - 1000 mg CIPRO<sup>®</sup> XR for 14 days in patients with mild renal impairment ( $CL_{cr}$  — mL/min)
  - 1000 mg CIPRO<sup>®</sup> XR for 14 days in patients with moderate renal impairment ( $CL_{cr}$  — 50 mL/min)
  - 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with severe renal impairment ( $CL_{cr}$  <30 mL/min)

- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with mild renal impairment ( $CL_{cr}$  — 50 mL/min)
- 500 mg CIPRO<sup>®</sup> XR for 14 days in patients with moderate renal impairment ( $CL_{cr}$  — 30 mL/min)
- 750 mg CIPRO<sup>®</sup> IR bid for 14 days in patients with normal renal function ( $CL_{cr}$  — 120 mL/min)

Based on the information obtained from the above-mentioned simulations, adjustments to the dosage regimen for CIPRO<sup>®</sup> XR 1000 mg in patients with mild and/or moderate renal impairment may be needed.

3. The applicant used the established relationship between clearance (CL) of intravenously administered ciprofloxacin and creatinine clearance ( $CL_{cr}$ ). However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of the orally administered Cipro IR tablet and use it for the purpose of modeling and simulations. We recommend that the applicant re-develop the relationship between oral ciprofloxacin clearance and creatinine clearance ( $CL_{cr}$ ) and compare with the previous results.

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