CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-473

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW

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

NDAs #: 21-473

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

SPONSOR: Bayer Pharmaceutical Division
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SUBMISSION REVIEWED: Original New Drug Application (CIPRO® —

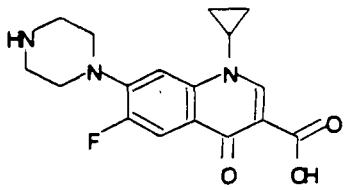
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Uncomplicated Urinary Tract Infections

DOSAGE FORM: 500-mg Tablets

DRUG PRODUCT NAME

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



Molecular Formula: $C_{17}H_{18}FN_3O_3$
Molecular Weight: —

SUPPORTING DOCUMENTS:

NDA #19-537—Bayer Ciprofloxacin Tablets—Approved October 22, 1987
NDA #19-847—Bayer Ciprofloxacin IV 1%–Approved December 26, 1990
NDA #19-857—Bayer Ciprofloxacin IV in 5% Dextrose—Approved December 26, 1990
NDA #19-858—Bayer Ciprofloxacin IV in 0.9% Saline—Approved December 26, 1990
NDA #20-780—Bayer Ciprofloxacin Oral Suspension—Approved September 26, 1997

BACKGROUND:

This application is for a new tablet formulation of ciprofloxacin. This new formulation is a once daily tablet. These ciprofloxacin 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 tablets result in a higher C_{max} and an equivalent AUC when compared to Cipro® Tablets for the same total dose (e.g. Ciprofloxacin 500 mg tablets compared to Cipro® 250 mg twice daily).

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

CONCLUSIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The required microbiology revisions are listed as recommendations at the end of this review on pages 14-17.

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EXECUTIVE SUMMARY

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

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

In Study 100346 CIPRO — tablets (500 mg once daily for 3 days) were compared with immediate-release ciprofloxacin tablets (250 mg twice daily for 3 days) in the treatment of uncomplicated urinary tract infections. The trial enrolled 905 patients. The primary endpoint was bacteriological eradication at 4-11 days post-therapy. The bacteriological eradication rate for CIPRO — tablets was 94.5% (188/199) compared to 93.7% (209/223) for the immediate release tablets. The eradication rates for individual pathogens are shown in TABLE A.

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

Pathogen	CIPRO — (500 mg QD)	Cipro Immediate Release (250 mg BID)
Escherichia coli	156/160 (97.5%)	176/181 (97.2%)
Enterococcus faecalis	10/11 (90.9%)	17/21 (81.0%)
Klebsiella pneumoniae	7/9 (77.8%)	11/14 (78.6%)
Proteus mirabilis	11/12 (91.7%)	7/7 (100%)
Staphylococcus saprophyticus	5/6 (83.3%)	7/7 (100%)

As usual in uncomplicated urinary tract infections, most of the pathogens were *Escherichia coli.* There were very few of the other pathogens detected in the clinical trial. Eradication rates were good for all five of the listed pathogens.

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

No new information has been submitted.

IN VITRO ACTIVITY AGAINST RECENT CLINICAL ISOLATES FROM UTIs

SURVEILLANCE STUDIES

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

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

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

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

The TSN™ Database-USA (—), provided national surveillance data for UTI isolates for the year 2000. More than 175 medical centers contributed to this database. TABLE 2 summarizes the *in vitro* activity of ciprofloxacin against the most common UTI pathogens during this time period.

TABLE 2
Ciprofloxacin Surveillance Data for UTI Isolates (TSN Database—2000)

Organism	Total Number	% Susceptible	% Intermediate	% Resistant
Escherichia coli	151,668	95.9	0.1	4.0
Klebsiella pneumoniae	26,040	95.4	0.6	4.0
Proteus mirabilis	15,764	86	1.2	12.9
Staphylococcus saprophyticus	1,139	98.6	0	1.4
Enterococcus faecalis	13,772	66.2	4.5	29.3

These data for the year 2000 are similar to those in the previous study for the end of 1999. Once again about 10% of *Proteus mirabilis* were resistant to ciprofloxacin. Almost 30% of *Enterococcus faecalis* isolates were resistant to ciprofloxacin. *Enterococcus faecalis* is approved for UTI in the present ciprofloxacin tablet label. It is listed in the microbiology subsection of the present ciprofloxacin tablet label with the qualifier that many strains are only moderately susceptible. [redacted] is proposed for the labeling of this product.

DATA FROM THE CLINICAL STUDY

This application has one pivotal study 100346. This was a Phase III, prospective, active-controlled, randomized, double-blind, multicenter study conducted in the United States in adult female patients with uncomplicated urinary tract infections. The main objective of the study was to compare the safety and efficacy of Ciprofloxacin [redacted] 500 mg oral tablets given once daily for 3 days with conventional, immediate-release ciprofloxacin tablets 250 mg given twice a day for 3 days. The primary efficacy was microbiological outcome at the test-of-cure visit (4 to 11 days post-treatment). Secondary efficacy parameters were microbiological outcome at the late follow-up visit (Day 25 to 50) and clinical outcome at both visits.

During the clinical study the susceptibility of the causative organisms was determined at the Central Laboratory [redacted]). Broth microdilution susceptibility tests were performed according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines. All causative organisms from the Ciprofloxacin [redacted] arm are listed in TABLE 3. *Escherichia coli* was the most frequently isolated organism (n=160), followed by *Proteus mirabilis* (n=12) and *Enterococcus faecalis* (n=11). The MIC_{90} for *E. coli* was 0.03 µg/mL, which is the same as for isolates of *E. coli* in the surveillance studies.

TABLE 3
MICs of Pre- therapy Isolates in Ciprofloxacin — Arm

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

PHARMACOKINETICS/BIOAVAILABILITY

The proposed dose is a single 500-mg tablet taken once a day for 3 days.

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

The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following 500 mg Ciprofloxacin — once daily is 7.97 mg.h/L. This is about equal to the AUC for immediate-release ciprofloxacin 250 mg given twice daily. The peak plasma concentration (C_{max}) of Ciprofloxacin — 500 mg given every 24 hours was 35% to 37% higher (Day 1 and Day 5, respectively) than the C_{max} following 250 mg immediate-release ciprofloxacin given every 12 hours. Median time to maximum plasma concentration (t_{max}) for Ciprofloxacin — was 1.5 hours under fasting conditions, which was comparable to that of immediate-release ciprofloxacin. The elimination half-lives of both formulations were approximately 5 hours. TABLE 4 compares the pharmacokinetic parameters at steady state for the two tablet formulations.

TABLE 4
Ciprofloxacin Pharmacokinetics (Mean ± Standard Deviation)

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

* median (range)

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

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

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

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

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

RESULTS FROM CLINICAL TRIAL

STUDY 100346

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE 10
Microbiological and Clinical Responses at Test-of-Cure in Ciprofloxacin — Arm

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

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

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

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

TABLE 11
Microbiological Responses by MIC

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

TABLE 11 (Continued)
Microbiological Responses by MIC

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

LABELING

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

The susceptibility testing section is basically identical to that in the ciprofloxacin tablet label, but has been amended to include only the sections pertinent to organisms that are indicated for UTI infections. The statement that introduces the interpretive criteria should be revised to state what organisms the criteria are for rather than what organisms the criteria are not appropriate for. The revised labeling, which should be sent to the applicant, is presented at the end of this review under RECOMMENDATIONS on pages 14-17.

REFERENCE

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

RECOMMENDATIONS

The sponsor should be notified of the following:

1. [redacted] s should be deleted from the listing of organisms with *in vitro* activity (list #2). These organisms are not usually associated with uncomplicated UTI infections.

2. [redacted] *s* should be revised to *Citrobacter koseri.*

3. In the Susceptibility Tests subsection the two sentences that read [redacted] should be revised to read "For testing Enterobacteriaceae, *Staphylococcus* species, and *Enterococcus* species."

4. The following statement should be added to the Diffusion Techniques subsection: "Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin."

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

MICROBIOLOGY
Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $<10^{-9}$ to 1×10^{-6}.

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

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

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

Aerobic gram-negative microorganisms
Escherichia coli

Proteus mirabilis

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

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

Aerobic gram-negative microorganisms

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

Susceptibility Tests
Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing [redacted] -Enterobacteriaceae,

Enterococcus species, and *Staphylococcus species*:

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

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

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

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

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

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

For testing [redacted] -Enterobacteriaceae,

Enterococcus species, and *Staphylococcus species*:

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

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

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

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

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ON ORIGINAL

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CONCURRENCES:

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