CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-847/ S-026
19-857 / S-028
19-858 / S-022

Trade Name: **Cipro**

Generic Name: **Ciprofloxacin**

Sponsor: **Bayer Corporation**

Approval Date: **April 17, 2002**

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APPLICATION NUMBER:

19-847/ S-026
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19-858 / S-022

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-847/S-026
NDA 19-857/S-028
NDA 19-858/S-022

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides
Assistant Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications dated January 11, 2001, received January 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg; CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg; and CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg.

We acknowledge receipt of your submissions dated February 4, 2002 and February 28, 2002.

Your submission of March 27, 2002 constituted a complete response to our January 31, 2002 action letter.

These supplements provide for the following changes to the Cipro® IV label. Deleted text is noted by ~~strikethrough~~ and added text is noted by double underline:

1. **DESCRIPTION**

- The following sentence was deleted from the second paragraph in this section:

  ~~"Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position."~~

- "Latex-free" was added to the following sentence to read:

  "The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride."

2. CLINICAL PHARMACOLOGY

•New subheadings (**Absorption, Distribution, Metabolism, Excretion** and **Special Populations)** were added to this section and existing information was reorganized under the new subheadings.

•The following senetnce concerning probenecid was deleted since the same information is stated in **PRECAUTIONS: Drug Interactions:**

> ~~"Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation.~~

•The following paragraph was added to read:

> "**Drug-drug Interactions:** The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)"

•The **Microbiology** subsection was completely revised.

3. INDICATIONS AND USAGE

•The **Lower Respiratory Infections** statement was revised to read:

> **"Lower Respiratory Infections** caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, or Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis."

•The references to **DOSAGE AND ADMINISTRATION** in the **Complicated intra-Abdominal Infections** and **Empirical Therapy for Febrile Neutropenic Patients** statements were deleted since this reference appears at the beginning of this section.

4. CLINICAL STUDIES

•The following demographics information for **Empirical Therapy for Febrile Neutropenic Patients** was deleted for brevity:

~~The demographics of the evaluable patients were as follows:~~

~~Total~~	~~Ciprofloxacin/Piperacillin N=233~~	~~Tobramycin/Piperacillin N=237~~
~~Median Age (years)~~	~~47.0 (range 19-84)~~	~~50.0 (range 18-81)~~

~~Male 114 (48.9%) 117 (49.4%)~~
~~Female 119 (51.1%) 120 (50.6%)~~
~~Leukemia/Bone Marrow Transplant 165 (70.8%) 158 (66.7%)~~
~~Solid Tumor/Lymphoma 68 (29.2%) 79 (33.3%)~~
~~Median Duration of Neutropenia (days) 15.0 (range 1-61) 14.0 (range 1-89)~~

5. **PRECAUTIONS**

•The **Information for Patients** subsection was revised to read:

Information For Patients: Patients should be advised:

- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

- that ciprofloxacin may cause dizziness and lightheadedness~~; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination~~

- ~~Patients should be advised~~ that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.

- ~~Patients should be advised~~ to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

- ~~Patients should be advised~~ that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

•The following two statements were moved from the **CLINICAL PHARMACOLOGY** section and added to the **Drug Interactions** subsection:

"The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly."

"Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 µg/mL ½ hour and 1.18 µg/mL between 6-8 hours after the end of infusion."

• At the end of the **Drug Interactions** subsection the following statement was deleted to be consistent with other quinolone labeling. It is also not a drug interaction:

~~" As with other broad-spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing are essential. If superinfection occurs during therapy, appropriate measures should be taken."~~

• The **Pregnancy: Teratogenic Effects. Pregnancy Category C** subsection was revised to read:

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones-(52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses ~~of up to 100mg/kg (0.8 and 0.4 times the maximum daily human dose based upon body surface area, respectively) and I.V. doses of up to 30 mg/kg (0.24 and 0.12 times~~ up to 100

mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. ~~There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~ (See **WARNINGS**.)

•The following sentence was added to the **Nursing Mothers** subsection and is now the second sentence:

"The amount of ciprofloxacin absorbed by the nursing infant is unknown."

6. **ADVERSE REACTIONS**

•The following sentence was moved and is now the last sentence in the first paragraph:

" Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment."

•The following events were moved from the third paragraph to the "additional events" table:

"HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time"

"MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis"

•The following post-marketing adverse events were changed from table format to paragraph format:

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:
change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of serum triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tedonitis/tendon rupture, vaginal candidiasis (See **PRECAUTIONS.)**

7. The **DOSAGE AND ADMINISTRATION** section was completely revised.

8. **HOW SUPPLIED**

•The third sentence in the first paragraph were revised to read:

"The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:

VIAL: manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220."

9. **STORAGE**

•The following USP statement was added to the end of this section:

"Ciprofloxacin is also available as CIPRO (ciprofloxacin HCl) Tablets 100, 250, 500, and 750 mg and CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition".

10. Three new references were added to the **REFERENCES** section.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions noted below. Accordingly, the supplemental applications are approved effective on the date of this letter.

1. As we discussed by telephone on April 17, 2002, the following sentences were inadvertently deleted from the **CLINICAL PHARMACOLOGY** section, **Excretion** subsection, and should be replaced:

> "Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (<1%) is recovered from the bile as unchanged drug. Approximately 15% of an I.V. dose is recovered from the feces within 5 days after dosing."

2. In the **CLINICAL PHARMACOLOGY** section, **Microbiology** subsection, "*Acinetobacter Iwoffii*" is spelled incorrectly. Replace 'Iwoffii" with "Iwoffi".

3. Please correct the spelling of the word "have" in the first sentence of the **WARNINGS** section to read as follows:

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), - EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy**, and **Nursing Mothers** subsections.)

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (package insert submitted March 27, 2002). These revisions are a term of the approval of these applications.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 19-847/S-026, NDA 19-857/S-028, NDA 19-858/S-022." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
4/17/02 05:11:32 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-847/ S-026
19-857 / S-028
19-858 / S-022

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-847/S-026
NDA 19-857/S-028
NDA 19-858/S-022

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides
Assistant Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Christoforides:

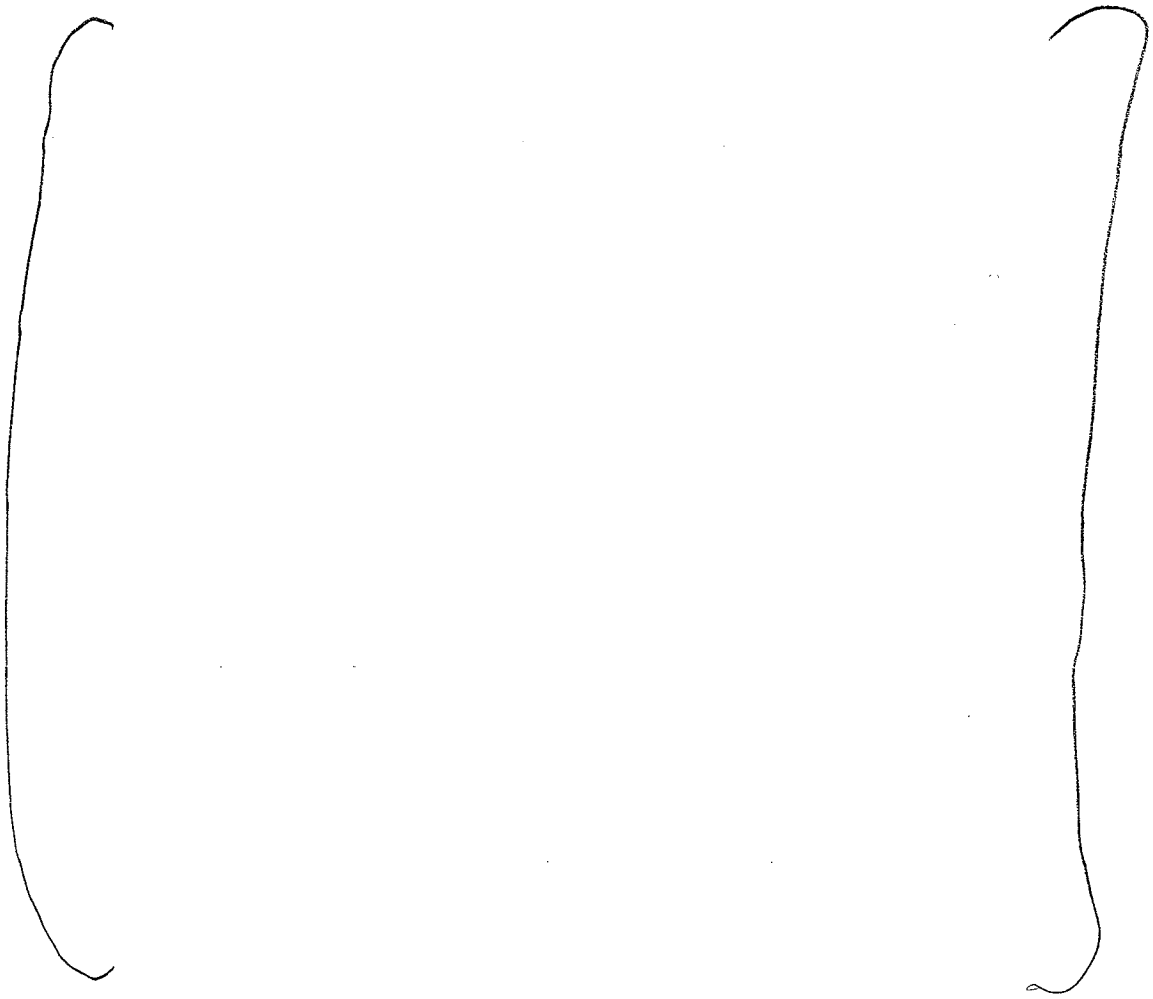
Please refer to your supplemental new drug applications dated January 11, 2001, received January 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg, CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg, and CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg.

We acknowledge receipt of your submission dated June 29, 2001.

These supplements propose the following change(s):
1. Multiple changes to the package insert to be more consistent with current labeling standards.
2. Length of the package insert shortened to make the package insert more physician friendly
3. Microbiology changes incorporated as proposed by the Agency

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved it will be necessary for you to submit draft labeling revised as follows [Note this revision was previously communicated in our fax dated December 19, 2001]:

PRECAUTIONS
Please replace the current wording with the following:



In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.
These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Renata Albrecht
1/31/02 03:29:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-847/ S-026
19-857 / S-028
19-858 / S-022

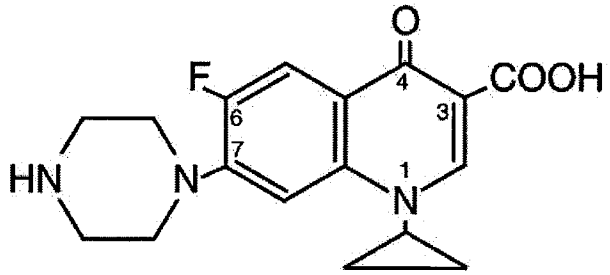
LABELING

CIPRO® I.V.
(ciprofloxacin)
For Intravenous Infusion

PZXXXXXX **2/02**

DESCRIPTION

CIPRO® I.V. (ciprofloxacin) is a synthetic broad-spectrum antimicrobial agent for intravenous (I.V.) administration. Ciprofloxacin, a fluoroquinolone, 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 chemical structure is:



Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 331.4. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in water and ethanol. CIPRO I.V. solutions are available as sterile 1.0% aqueous concentrates, which are intended for dilution prior to administration, and as 0.2% ready-for-use infusion solutions in 5% Dextrose Injection. All formulas contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1% aqueous concentrates in vials is 3.3 to 3.9. The pH range for the 0.2% ready-for-use infusion solutions is 3.5 to 4.6.

The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di(2-ethylhexyl) phthalate (DEHP), up to 5 parts per million. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Absorption

Following 60-minute intravenous infusions of 200 mg and 400 mg ciprofloxacin to normal volunteers, the mean maximum serum concentrations achieved were 2.1 and 4.6 µg/mL, respectively; the concentrations at 12 hours were 0.1 and 0.2 µg/mL, respectively.

Steady-state Ciprofloxacin Serum Concentrations (µg/mL) After 60-minute I.V. Infusions q 12 h.

	Time after starting the infusion					
Dose	**30 min.**	**1 hr**	**3 hr**	**6 hr**	**8 hr**	**12 hr**
200 mg	1.7	2.1	0.6	0.3	0.2	0.1
400 mg	3.7	4.6	1.3	0.7	0.5	0.2

The pharmacokinetics of ciprofloxacin are linear over the dose range of 200 to 400 mg administered intravenously. Comparison of the pharmacokinetic parameters following the 1st and 5th I.V. dose on a q 12 h regimen indicates no evidence of drug accumulation.

The absolute bioavailability of oral ciprofloxacin is within a range of 70-80% with no substantial loss by first pass metabolism. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500-mg oral dose given every 12 hours. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 8 hours has been shown to produce an AUC at steady-state equivalent to that produced by a 750-mg oral dose given every 12 hours. A 400-mg I.V. dose results in a Cmax similar to that observed with a 750-mg oral dose. An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250-mg oral dose given every 12 hours.

Steady-state Pharmacokinetic Parameter Following Multiple Oral and I.V. Doses

Parameters	500 mg q12h, P.O.	400 mg 12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC (µg•hr/mL)	13.7[a]	12.7[a]	31.6[b]	32.9[c]
C_{max}(µg/mL)	2.97	4.56	3.59	4.07

[a] AUC_{0-12h} [b] $AUC_{24h}=AUC_{0-12h}x2$ [c] $AUC_{24h}=AUC_{0-8h}x3$

Distribution

After intravenous administration, ciprofloxacin is present in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. It has also been detected in the lung, skin, fat, muscle, cartilage, and bone. Although the drug diffuses into cerebrospinal fluid (CSF), CSF concentrations are generally less than 10% of peak serum concentrations. Levels of the drug in the aqueous and vitreous chambers of the eye are lower than in serum.

Metabolism

After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose. The binding of ciprofloxacin to serum proteins is 20 to 40%.

Excretion

The serum elimination half-life is approximately 5-6 hours and the total clearance is around 35 L/hr. After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. Following a 200-mg I.V. dose, concentrations in the urine usually exceed 200 µg/mL 0-2 hours after dosing and are generally greater than 15 µg/mL 8-12 hours after dosing. Following a 400- mg I.V. dose, urine concentrations generally exceed 400 µg/mL 0-2 hours after dosing and are usually greater that 30 µg/mL 8-12 hours after dosing. The renal clearance is approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Special Populations

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

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged and dosage adjustments may be required. (See **DOSAGE AND ADMINSTRATION**.)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. However, the kinetics of ciprofloxacin in patients with acute hepatic insufficiency have not been fully elucidated.

Drug-drug Interactions: The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

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

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO I.V. (ciprofloxacin for intravenous infusion).

Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

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 ciprofloxacin intravenous formulations in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic gram-negative microorganisms

Acinetobacter lwoffii
Aeromonas hydrophila
Campylobacter jejuni
Edwardsiella tarda
Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Neisseria gonorrhoeae
Pasteurella multocida
Salmonella enteritidis
Salmonella typhi
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

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 aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*[a]:

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

[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [b]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible " category should be submitted to a reference laboratory for further testing.

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

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

Organism		**MIC (µg/mL)**
E. faecalis	ATCC 29212	0.25-2.0
E. coli	ATCC 25922	0.004-0.015
H. influenzae[a]	ATCC 49247	0.004-0.03
P. aeruginosa	ATCC 27853	0.25-1.0
S. aureus	ATCC 29213	0.12-0.5

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

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 aerobic microorganisms other than *Haemophilus influenzae,* and *Haemophilus parainfluenzae* [a]:

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

[a] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	Interpretation
≥21	Susceptible (S)

[b] This zone diameter standard is applicable only to tests *with Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[2].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

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

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

Organism		Zone Diameter (mm)
E. coli	ATCC 25922	30-40
H. influenzae[a]	ATCC 49247	34-42
P. aeruginosa	ATCC 27853	25-33
S. aureus	ATCC 25923	22-30

[a]These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)[2].

INDICATIONS AND USAGE

CIPRO I.V. is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below when the intravenous administration offers a route of administration advantageous to the patient. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Urinary Tract Infections caused by *Escherichia coli* (including cases with secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus, or Enterococcus faecalis.*

Lower Respiratory Infections caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, or Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

Nosocomial Pneumonia caused by *Haemophilus influenzae or Klebsiella pneumoniae.*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin susceptible), *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Complicated Intra-Abdominal Infections (used in conjunction with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

Acute Sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae*, or *Moraxella catarrhalis*.

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*.

Empirical Therapy for Febrile Neutropenic Patients in combination with piperacillin sodium. (See **CLINICAL STUDIES**.)

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4] (See also, **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO I.V. may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CLINICAL STUDIES

EMPIRICAL THERAPY IN FEBRILE NEUTROPENIC PATIENTS

The safety and efficacy of ciprofloxacin, 400 mg I.V. q 8h, in combination with piperacillin sodium, 50 mg/kg I.V. q 4h, for the empirical therapy of febrile neutropenic patients were studied in one large pivotal multicenter, randomized trial and were compared to those of tobramycin, 2 mg/kg I.V. q 8h, in combination with piperacillin sodium, 50 mg/kg I.V. q 4h.

Clinical response rates observed in this study were as follows:

Outcomes	**Ciprofloxacin/Piperacillin N=233 Success (%)**	**Tobramycin/Piperacillin N=237 Success (%)**
Clinical Resolution of Initial Febrile Episode with No Modifications of Empirical Regimen*	63 (27.0%)	52 (21.9%)
Clinical Resolution of Initial Febrile Episode Including Patients with Modifications of Empirical Regimen	187 (80.3%)	185 (78.1%)
Overall Survival	224 (96.1%)	223 (94.1%)

*To be evaluated as a clinical resolution, patients had to have: (1) resolution of fever; (2) microbiological eradication of infection (if an infection was microbiologically documented); (3) resolution of signs/symptoms of infection; and (4) no modification of empirical antibiotic regimen.

CONTRAINDICATIONS

CIPRO I.V. (ciprofloxacin) is contraindicated in persons with history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), - EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVEN NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.) Ciprofloxacin causes lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY.**)

Convulsions, increased intracranial pressure and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interaction** and **ADVERSE REACTIONS.**)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF INTRAVENOUS CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse events have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been reported extremely rarely in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were

related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

PRECAUTIONS

General: INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINSTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local I.V. site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used. (See **ADVERSE REACTIONS**.)

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS, Information for Patients**, and **Drug Interactions**.)

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See **ANIMAL PHARMACOLOGY**.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See **DOSAGE AND ADMINISTRATION**.)

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in some patients who were exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Information For Patients: Patients should be advised:

- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

- that ciprofloxacin may cause dizziness and lightheadedness.

- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.

- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See **WARNINGS.**) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and prolongation of its serum half-life.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, in some patients, resulted in severe hypoglycemia. Fatalities have been reported.

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 µg/mL ½hour and 1.18 µg/mL between 6-8 hours after the end of infusion.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin. Test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.[3]

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the highest recommended human dose of 1200 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones-(52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, fetal distress, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures). [9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See **WARNINGS**.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made

whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established, except for use in inhalational anthrax (post-exposure). Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION** and **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3 mg/kg/dose q8h for a total of 10 - 21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

Geriatric Use: In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function.

However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTATION.**)

ADVERSE REACTIONS

The most frequently reported events, without regard to drug relationship, among patients treated with intravenous ciprofloxacin were nausea, diarrhea, central nervous system disturbance, local I.V. site reactions, abnormalities of liver associated enzymes (hepatic enzymes), and eosinophilia. Headache, restlessness, and rash were also noted in greater than 1% of patients treated with the most common doses of ciprofloxacin. Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

Local I.V. site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Additional events, without regard to drug relationship or route of administration, that occurred in 1% or less of ciprofloxacin patients are listed below:

CARDIOVASCULAR: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris

CENTRAL NERVOUS SYSTEM: convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy

GASTROINTESTINAL: ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric or abdominal pain, vomiting, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence

HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time

I.V. INFUSION SITE: thrombophlebitis, burning, pain, pruritus, paresthesia, erythema, swelling

MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis

RENAL/UROGENITAL: renal failure, interstitial nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis. Crystalluria, cylindruria, hematuria and albuminuria have also been reported.

RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea, pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough

SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae,

hands or lower extremities, purpura, fever, chills, flushing, pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, photosensitivity (See **WARNINGS.**)
SPECIAL SENSES: decreased visual acuity, blurred vision, disturbed vision (flashing lights, change in color perception, overbrightness of lights, diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmus, a bad taste

In several instances, nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin (I.V. and I.V. P.O. sequential) with intravenous beta-lactam control antibiotics, the CNS adverse event profile of ciprofloxacin was comparable to that of the control drugs.

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:
change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of serum triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tedinitis/tendon rupture, vaginal candidiasis (See **PRECAUTIONS.**)

Adverse Laboratory Changes: The most frequently reported changes in laboratory parameters with intravenous ciprofloxacin therapy, without regard to drug relationship are listed below:

Hepatic -	elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, and serum bilirubin;
Hematologic -	elevated eosinophil and platelet counts, decreased platelet counts, hemoglobin and/or hematocrit;
Renal -	elevations of serum creatinine, BUN, and uric acid;
Other -	elevations of serum creatine phosphokinase, serum theophylline (in patients receiving theophylline concomitantly), blood glucose, and triglycerides.

Other changes occurring infrequently were: decreased leukocyte count, elevated atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation of serum gamma-glutamyl transpeptidase (gamma GT), decreased BUN, decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum potassium, elevated serum cholesterol. Other changes occurring rarely during administration of ciprofloxacin were: elevation of serum amylase, decrease of blood glucose, pancytopenia, leukocytosis, elevated sedimentation rate, change in serum phenytoin, decreased prothrombin time, hemolytic anemia, and bleeding diathesis.

OVERDOSAGE

In the event of acute overdosage, the patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

DOSAGE AND ADMINISTRATION

CIPRO I.V. should be administered by intravenous infusion over a period of 60 minutes at dosages described in the Dosage Guidelines table. Slow infusion of a dilute solution into a larger vein will minimize patient discomfort and reduce the risk of venous irritation. (See **Preparation of CIPRO I.V. for Administration section**.)

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative microorganism, the integrity of the patient's host-defense mechanisms, and the status of renal and hepatic function.

DOSAGE GUIDELINES

Intravenous

Infection†	Type or Severity	Unit Dose	Frequency	Usual Duration
Urinary Tract	Mild/Moderate	200 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q12h	7-14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10-14 Days
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4-6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4-6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7-14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe			
	Ciprofloxacin +	400 mg	q8h	7-14 Days
	Piperacillin	50 mg/kg Not to exceed 24 g/day	q4h	
Inhalational anthrax (post-exposure)**	Adult	400 mg	q12h	60 Days
	Pediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q12h	60 Days

* used in conjunction with metronidazole. (See product labeling for prescribing information.)

†DUE TO THE DESIGNATED PATHOGENS (See **INDICATIONS AND USAGE**.)

** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum

concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.** Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

CIPRO I.V. should be administered by intravenous infusion over a period of 60 minutes.

CIPRO Tablets and CIPRO Oral Suspension for oral administration are available. Parenteral therapy may be switched to oral CIPRO when the condition warrants, at the discretion of the physician. (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens.)

Equivalent AUC Dosing Regimens

CIPRO Oral Dosage	Equivalent CIPRO I.V. Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Impaired Renal Function: The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dosage
>30	See usual dosage.
5-29	200-400 mg q 18-24 hr

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance:

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

Preparation of CIPRO I.V. for Administration

Vials (Injection Concentrate): THIS PREPARATION MUST BE DILUTED BEFORE USE. The intravenous dose should be prepared by aseptically withdrawing the

concentrate from the vial of CIPRO I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1-2mg/mL. (See **COMPATIBILITY AND STABILITY.**) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of CIPRO I.V. If the concomitant use of CIPRO I.V. and another drug is necessary each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Flexible Containers: CIPRO I.V. is also available as a 0.2% premixed solution in 5% dextrose in flexible containers of 100 mL or 200 mL. The solutions in flexible containers do not need to be diluted and may be infused as described above.

COMPATIBILITY AND STABILITY

Ciprofloxacin injection 1% (10 mg/mL), when diluted with the following intravenous solutions to concentrations of 0.5 to 2.0 mg/mL, is stable for up to 14 days at refrigerated or room temperature storage.

0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
Sterile Water for Injection
10% Dextrose for Injection
5% Dextrose and 0.225% Sodium Chloride for Injection
5% Dextrose and 0.45% Sodium Chloride for Injection
Lactated Ringer's for Injection

HOW SUPPLIED

CIPRO I.V. (ciprofloxacin) is available as a clear, colorless to slightly yellowish solution. CIPRO I.V. is available in 200 mg and 400 mg strengths. The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:

VIAL: manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220.

SIZE	STRENGTH	NDC NUMBER
20 mL	200 mg, 1%	0026-8562-20
40 mL	400 mg, 1%	0026-8564-64

FLEXIBLE CONTAINER: manufactured for Bayer Corporation by Abbott Laboratories, North Chicago, IL 60064.

SIZE	STRENGTH	NDC NUMBER
100 mL 5% Dextrose	200 mg, 0.2%	0026-8552-36
200 mL 5% Dextrose	400 mg, 0.2%	0026-8554-63

FLEXIBLE CONTAINER: manufactured for Bayer Corporation by Baxter Healthcare Corporation, Deerfield, IL 60015.

SIZE	STRENGTH	NDC NUMBER
100 mL 5% Dextrose	200 mg, 0.2%	0026-8527-36
200 mL 5% Dextrose	400 mg, 0.2%	0026-8527-63

STORAGE

Vial: Store between 5-30°C (41-86°F).
Flexible Container: Store between 5-25°C (41-77°F).

Protect from light, avoid excessive heat, protect from freezing.

CIPRO I.V. (ciprofloxacin) is also available in a 120 mL Pharmacy Bulk Package.

Ciprofloxacin is also available as CIPRO (ciprofloxacin HCl) Tablets 100, 250, 500, and 750 mg and CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension.

* Does not comply with USP.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS.**) Damage of weight-bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin given daily for 4 weeks caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight-bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after intravenous doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In dogs, ciprofloxacin administered at 3 and 10 mg/kg by rapid intravenous injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release because they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid intravenous injection also produces hypotension, but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs, such as phenylbutazone and indomethacin, with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity, seen with some related drugs, has not been observed in ciprofloxacin-treated animals.

INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving oral and intravenous regimens. (See **DOSAGE AND ADMINISTRATION**.) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady-state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/ml, and 4.56 µg/ml following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for both of these regimens is 0.2 µg/ml. In a study of 10 pediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to pediatric patients are limited. (For additional information, see **PRECAUTIONS, Pediatric Use**.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4]

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/ml. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected Tmax (1 hour post-dose) following oral dosing to steady-state ranged from 0.98 to 1.69 µg/ml. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/ml[5]. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.[6]

References:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fifth Edition. Approved Standard NCCLS Document M7- A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January, 2000.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests - Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.
3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Products Advisory Committee Meeting, March 31, 1993, Silver Spring MD. Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA.
4. 21 CFR 314.510 (Subpart H – Accelerated Approval of New Drugs for Life-Threatening Illnesses).
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7. Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.

8. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6): 1336-1339.

9. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure . Evaluation of a case registry of the European network of teratology information services (ENTIS). Eur J Obstet Gynecol Reprod Biol. 1996;69:83-89.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-847/ S-026
19-857 / S-028
19-858 / S-022

MEDICAL REVIEW(S)

NDA 19-537/S-041, NDA 20-780/S-011
NDA 19-847/S-026, NDA 19-857/S-028, NDA 19-858/S-022

Labeling and Clinical Review of Supplemental Labeling Revisions (SLR):

Materials Reviewed:

Product	NDA #	SLR #	Letter Date	Receipt Date	Completed Date
CIPRO® (ciprofloxacin) Tablets, 100 mg, 250 mg, 500 mg, 750 mg	19-537	041	December 22, 2000	December 26, 2000	January 30, 2002
Amendment:	19-537	041	June 22, 2001	June 25, 2001	January 30, 2002
CIPRO® (ciprofloxacin) Oral Suspension, 5% and 10%, 250 mg, 500 mg	20-780	011	December 22, 2000	December 26, 2000	January 30, 2002
Amendment:	20-780	011	June 22, 2001	June 25, 2001	January 30, 2002
CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg	19-847	026	January 11, 2001	January 12, 2001	January 30, 2002
Amendment:	19-847	026	June 29, 2001	July 2, 2001	January 30, 2002
CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg	19-857	028	January 11, 2001	January 12, 2001	January 30, 2002
Amendment:	19-857	028	June 29, 2001	July 2, 2001	January 30, 2002
CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg (never launched)	19-858	022	January 11, 2001	January 12, 2001	January 30, 2002
Amendment:	19-858	022	June 29, 2001	July 2, 2001	January 30, 2002

- Approved package insert for NDAs 19-537 and 20-780 dated August 30, 2000
- Approved package insert for NDAs 19-847 and 19-857 dated August 30, 2000
- FDA fax to Bayer concerning proposed Microbiology labeling revisions dated June 29, 2000
- FDA fax to Bayer concerning miscellaneous proposed labeling revisions dated March 5, 2001
- FDA fax to Bayer concerning FDA's s recommended pregnancy labeling revisions dated December 19, 2001
- FDA fax to Bayer concerning proposed Patient Information section (PPI) revisions dated January 14, 2002

Sponsor: Bayer Corporation Pharmaceutical Division

Background:
Cipro Tablet/Oral Suspension:
Ciprofloxacin (CIPRO®) is a flouroquinolone antibacterial agent. NDA 19-537 (tablet) was originally approved on October 22, 1987. NDA 20-780 (oral suspension) was originally approved on September 26, 1997. The tablet and oral suspension have shared one label since that time. The most recent labeling approval for these NDAs occurred on August 30,2000. No other labeling changes have been approved since that date.

Cipro IV Formulation:
NDA 19-847 (IV/vial) , NDA 19-857 (IV/Flexibag with Dextrose) and NDA 19-858 (IV/Flexibag with NaCl) were originally approved on December 26, 1990. The IV/vial and the IV/flexibag with Dextrose have shared a label since that time. The last approved labeling changes occurred on August 30, 2000. No other labeling changes have been approved since that time. The IV/Flexibag with NaCl was never launched by the company, and does not currently appear in the IV labeling.

These labeling supplements for prior approval submitted to all of the Cipro NDAs noted above in December 2000/January 2001 provide for multiple changes to the package inserts in order to be more consistent with current labeling standards. The length was shortened to "make the package insert more physician friendly while maintaining all pertinent and required information." Microbiology labeling changes proposed by Peter Dionne, Microbiology Reviewer and faxed to the company on June 29, 2000 were also included in these submissions. A new Patient Information section (PPI) was also added.

Following the initial review of these labeling supplements by Dr. Eileen Navarro, Medical Officer and Mr. Dionne's Microbiology review dated February 9, 2001, the following revisions were proposed for the Cipro labels. These were faxed to Bayer on March 5, 2001:

Clinical Reviewer Comments:

1. The clinical pharmacology section should be revised to include information in the following subsections: *Absorption, Distribution, Metabolism, Excretion, Special Populations*

2. The order of the approved indications should be maintained as in the original label.

3. The spelling of Administration in Line 926 should be corrected.

4. The equivalent oral and IV doses should be displayed in a table, following lines 985-7.

5. The section "Instructions to the Pharmacist" and "Instructions to the Patient" should be retained in its original location in the label.

6. The Clinical Studies section should be retained.

Microbiology Reviewer Comments:

7. In line 171 the words In vitro should be in italic in the sentence that begins "In vitro resistance to ciprofloxacin develops slowly ...

8. *Staphylococcus aureus* and *Staphylococcus epidermidis* in lines 192 and 193 should be qualified as (methicillin-susceptible strains only) instead of

9. *Streptococcus pneumoniae* in lines 195 and 249 should be qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the label instead of

Revised labels for the Cipro NDAs incorporating the proposed FDA revisions noted in the March 5, 2001 fax were submitted by Bayer on June 22, 2001, received June 25, 2001.

Electronic Labeling Comparisons:

Strikeout=deleted
Double underline=added

Cipro Tablet/Oral Suspension label
The approved package insert for NDA 19-537 (Tablet) and NDA 20-780 (Oral Suspension) dated August, 2000 was electronically compared to the proposed draft labeling dated June 22, 2001, received June 25, 2001. The changes were as follows:

1. **DESCRIPTION**
•The description of tablet color and the addition of "corn" to the word "starch" were added as follows:

> Ciprofloxacin tablets are white to slightly yellowish. CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

2. **CLINICAL PHARMACOLOGY**
•As we requested, new subheadings were added to this section and existing information was reorganized under the following; **Absorption, Distribution, Metabolism, Excretion** and **Special Populations.**

•Under **Absorption**, the following sentence was added and is now the third sentence in the second paragraph:

> The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

•The **Microbiology** subsection was revised as follows:

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

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.

[ ]

Moved from lines 274-277 pursuant to Peter Dionne's comments dated 6/29/00

[ ]

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO — (ciprofloxacin) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Pursuant to Peter Dionne's comments dated 6/29/00

Aerobic gram-negative microorganisms

Campylobacter jejuni	*Proteus mirabilis*
Citrobacter diversus	*Proteus vulgaris*
Citrobacter freundii	*Providencia rettgeri*
Enterobacter cloacae	*Providencia stuartii*
Escherichia coli	*Pseudomonas aeruginosa*
Haemophilus influenzae	*Salmonella typhi*
Haemophilus parainfluenzae	*Serratia marcescens*
Klebsiella pneumoniae	*Shigella boydii*
Moraxella catarrhalis	*Shigella dysenteriae*
Morganella morganii	*Shigella flexneri*
Neisseria gonorrhoeae	*Shigella sonnei*

[ ]

[ ]

[ ]

Delete I.V. microorganisms as this is only the PI for tablets and oral suspension

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

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 ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains only)

Pursuant to Peter Dionne's comments dated 6/29/00

Aerobic gram-negative microorganisms

Acinetobacter Iwoffii	*Pasteurella multocida*
Aeromonas hydrophila	*Salmonella enteritidis*
Edwardsiella tarda	*Vibrio cholerae*
Enterobacter aerogenes	*Vibrio parahaemolyticus*
Klebsiella oxytoca	*Vibrio vulnificus*
Legionella pneumophila	*Yersinia enterocolitica*

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

[ ]

Moved to Lines 185-187 and 182-183 pursuant to Peter Dionne's comments dated 6/29/00

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 aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

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

[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible " category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*[c]:

MIC (µg/mL)	Interpretation
≤ 0.06	Susceptible (S)
0.12 – 0.5	Intermediate (I)
≥ 1	Resistant (R)

Pursuant to Peter Dionne's comments dated 6/29/00

[c] This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

Delete pursuant to Peter Dionne's comments dated 6/29/00

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

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

Organism		MIC (µg/mL)
E. faecalis	ATCC 29212	0.25-2.0
E. coli	ATCC 25922	0.004-0.015
H. influenzae[a]	ATCC 49247	0.004-0.03
N. gonorrhoeae[b]	ATCC 49226	0.001-0.008
P. aeruginosa	ATCC 27853	0.25-1.0
S. aureus	ATCC 29213	0.12-0.5

[a]This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]

[b]This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base and 1% defined growth supplement.

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 aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

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

[a]These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	Interpretation
=21	Susceptible (S)

[b]This zone diameter standard is applicable only to tests *with Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*[c]:

Zone Diameter (mm)	Interpretation
≥ 41	Susceptible (S)
28 – 40	Intermediate (I)
≤ 27	Resistant (R)

Pursant to Peter Dionne's comments dated 6/29/00

[c]This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

Delete pursuant to Peter Dionne's comments dated 6/29/00

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin. As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Organism		**Zone Diameter (mm)**
E. coli	ATCC 25922	30-40
H. influenzae[a]	ATCC 49247	34-42
N. gonorrhoeae[b]	ATCC 49226	48-58
P. aeruginosa	ATCC 27853	25-33
S. aureus	ATCC 25923	22-30

[a] These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM).[2]

[b] These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

3. INDICATIONS AND USAGE

•As we requested, the order of the following indications was revised as follows:

Reorganized the order of the indications. No text has been added or deleted

Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.* (See **DOSAGE AND ADMINSTRATION.)**

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*

Lower Respiratory Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

Acute Sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae,* or *Moraxella catarrhalis.*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused *by Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.* (See **DOSAGE AND ADMINSTRATION.)**

[redacted]

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii*, Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei** when antibacterial therapy is indicated.

Pursuant to Peter Dionne's comments dated 6/29/00

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi.*

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae.*

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4] (See also, **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

Combined lines 495-504 into one paragraph

4. **PRECAUTIONS**

•The following paragraph was deleted in the **Drug Interactions** subsection to be consistent with other quinolone labeling:

[redacted]

5. **ADVERSE REACTIONS**

•The following sentence was moved from the fourth paragraph to the first paragraph which now reads:

[redacted]

•The following adverse events were added and this subsection now reads:

BODY AS A WHOLE: foot pain
CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis
CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia (See above.) (See **PRECAUTIONS**.)
GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic jaundice has been reported.
HEMIC/LYMPHATIC: lymphadenopathy
MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout

Added events from lines 850-856 that were not included in this list

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain
RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism
SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.) Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See **WARNINGS.**)
SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste

•In the **Post-Marketing Adverse Events** subsection, the following paragraph was added to replace the list of adverse events that previously existed (to be consistent with other quinolone labeling):

Change in serum phenytoin, postural hypotension, vasculitis, agitation, confusion, delirium, dysphagia, myoclonus, nystagmus, toxic psychosis, constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time, myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture, albuminuria, candiduria, renal calculi, vaginal candidiasis, anaphylactic reactions, erythema, multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, ansomia, taste loss, and elevation of serum triglycerides, cholesterol, blood glucose, or serum potassium. (See **PRECAUTIONS.**)

6. **OVERDOSAGE**
•The following sentence was moved from the end of this section and is now the ——— paragraph:

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

7. **DOSAGE AND ADMINISTRATION**
•The following text was deleted from this section and a sentence was added since the Dosage Guidelines Table incorporates the same information:

Cipro Tablets and Oral Suspension should be administered orally as described in the Dosage Guidelines table.

[redacted]

In order to shorten the length of the PI, delete text since Dosage Guideline Table incorporates the same information

[redacted]

•The following sentences were moved from the end to the beginning of this section and now appear before the Dosage Guidelines table. The last two paragraphs were combined into one as follows:

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection.

Moved up from lines 1018-1034 (Note: last two paragraphs were combined into one

[redacted]

•The Dosage Guidelines table was revised to mirror the new revised order of indications as follows:

DOSAGE GUIDELINES

Infection Durations†	Type or Severity	Unit Dose	Frequency	Usual
Urinary Tract	Acute Uncomplicated	100-mg or 250-m	q 12 h	3 Days
	Mild/Moderate	250-mg	q 12 h	7 to 14 Days
	Severe/Complicated	500-mg	q 12 h	7 to 14 Days
Chronic Bacterial Prostatitis	Mild/Moderate	500-mg	q 12 h	28 Days
Lower Respiratory	Mild/Moderate	500-mg	q 12 h	7 to 14 days

Revised table to mirror Dosage & Administration section's order of indications. No text has been added or deleted.

Tract	Severe/Complicated	750-mg	q 12 h	7 to 14 days
Acute Sinusitis	Mild/Moderate	500-mg	q 12 h	10 days
Skin and Skin Structure	Mild/Moderate	500-mg	q 12 h	7 to 14 Days
	Severe/Complicated	750-mg	q 12 h	7 to 14 Days
Bone and Joint	Mild/Moderate	500-mg	q 12 h	≥ 4 to 6 weeks
	Severe/Complicated	750-mg	q 12 h	≥ 4 to 6 weeks
Intra-Abdominal*	Complicated	500-mg	q 12 h	7 to 14 Days
Infectious Diarrhea	Mild/Moderate/Severe	500-mg	q 12 h	5 to 7 Days
Typhoid Fever	Mild/Moderate	500-mg	q 12 h	10 Days
Urethral and Cervical Gonococcal Infections	Uncomplicated	250-mg	single dose	single dose
Inhalational anthrax (post-exposure)**	Adult	500-mg	q 12 h	60 Days
	Pediatric	15 mg/kg per dose, not to exceed 500-mg per dose	q 12 h	60 Days

* used in conjunction with metronidazole
† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).
** Drug administration should begin as soon as possible after suspected or confirmed exposure.
This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.**

•The following sentence and table was added after the Dosing Guidelines table:

Patients whose therapy is started with CIPRO I.V. may be switched to CIPRO Tablets or Oral Suspension when clinically indicated at the discretion of the physician (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens).

New text

Equivalent AUC Dosing Regimens

Cipro Oral Dosage	Equivalent Cipro I.V Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

Pursuant to 3/5/01 FDA comments

•The following instructions for Cipro Oral Suspension were moved to **Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension:**

See Instructions for USE/HANDLING.

[redacted]

Moved instructions for oral suspension to lines 1245-1255

[redacted]

Moved to lines 1274-1275

•The second sentence under **Impaired Renal Function** was revised as follows:

These alternative [redacted] pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment.

8. **HOW SUPPLIED**

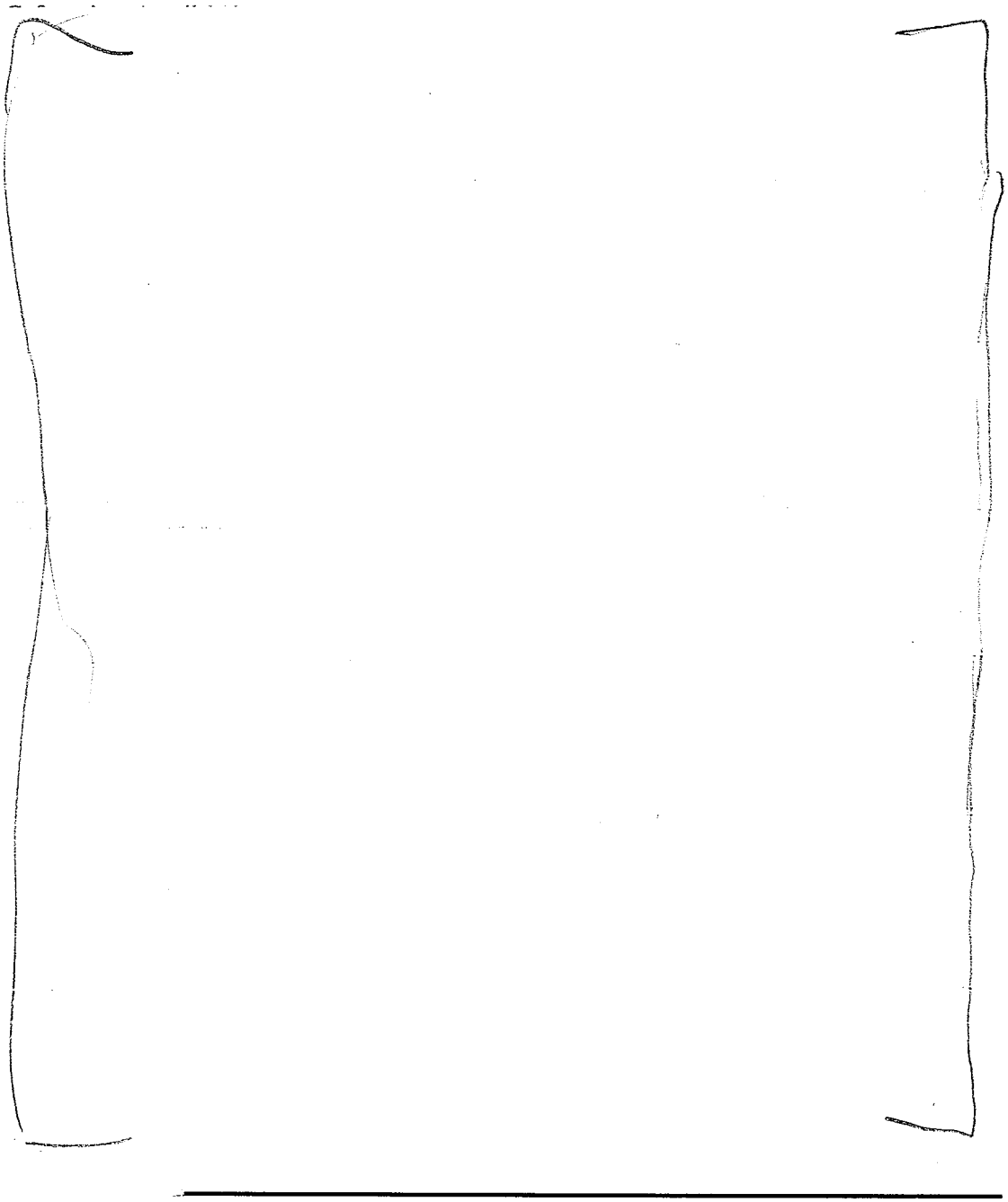
•The paragraph and table concerning Cipro Oral Suspension were revised as follows:

CIPRO [redacted] Oral Suspension is supplied in 5% [redacted] and 10% [redacted] strengths. The drug product is composed of two components (microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist. [redacted] See Instructions To The Pharmacist For Use/Handling.

Strengths	Total volume after reconstitution	Ciprofloxacin Concentration [redacted]	Ciprofloxacin contents per bottle	*NDC Code*
5%	100 mL	250 mg/5 mL	5,000 mg	0026-8551-36
10%	100 mL	500 mg/5 mL	10,000 mg	0026-8553-36

9. As we agreed, the **CLINICAL STUDIES** section was deleted as follows:

[redacted]



10. **Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension**

•The following information was moved/added to the beginning of this section:

CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g ciprofloxacin in 100 mL) strengths. The drug product is composed of two components (microcapsules and diluent) which must be combined prior to dispensing.

One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250-mg of ciprofloxacin.

One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500-mg of ciprofloxacin.

Appropriate Dosing Volumes of the Oral Suspensions:

New text.

Dose	5%	10%
250-mg	5 mL	2.5 mL
500-mg	10 mL	5 mL
750-mg	15 mL	7.5 mL

Moved from lines 1000-1010

•The following sentence was moved to this section:

CIPRO 5% and 10% Oral Suspension should not be administered through feeding tubes due to its physical characteristics.

•The following sentence was revised to read:

11. **PATIENT INFORMATION ABOUT**
CIPRO® (ciprofloxacin hydrochloride) TABLETS
CIPRO (ciprofloxacin) 5% and 10% ORAL SUSPENSION

Include Patient Information About Section

•This new section was added as follows:

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. The medicine described here can be prescribed only by a licensed health care professional. If you have questions, talk with your health care professional. Only your health care professional can determine if CIPRO is right for you.

What is CIPRO?

CIPRO is an antibiotic. It kills many kinds of bacteria that can cause infections of the bladder, kidney, prostate, cervix, stomach, intestines, lungs, sinus, bone, and skin. CIPRO has been shown in many clinical trials to be effective in the treatment of bacterial infections. As with all antibiotics, CIPRO is not effective in treating infections caused by viruses, such as the common cold or the flu. You should contact your doctor if you think your condition is not improving while taking CIPRO.

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:
Unless directed otherwise by your physician, CIPRO should be taken twice a day, at approximately the same time, in the morning and in the evening.

milk). You should take CIPRO for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection.

CIPRO Oral Suspension:
Take CIPRO Oral Suspension in the same way as above. In addition, remember to shake the bottle vigorously each time before use for approximately 15 seconds to make sure the suspension is mixed well. Be sure to swallow the required amount of suspension.

Who should not take CIPRO?

You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones".

In general, CIPRO is not recommended

What are the possible side effects of CIPRO?

CIPRO is generally well-tolerated. The most common side effects caused by CIPRO, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or other sources of ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking CIPRO.

CIPRO has been rarely associated with inflammation of tendons. If you pain, swelling, or rupture of a tendon, you should stop taking CIPRO and call your health care professional.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

Some antacids and multivitamins can interfere with the absorption of CIPRO and may prevent it from working. You should take CIPRO either 2 hours before or 6 hours after taking products that contain aluminum, calcium, iron, magnesium, or zinc.

Tell you health care provider if you are taking any theophylline products before starting CIPRO. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO. Inform your health care professional of all medications you're taking.

Remember:

- Take your dose of CIPRO in the morning and in the evening.
- Complete the course of CIPRO even if you are feeling better.
- Keep CIPRO and all medications out of reach of children.
- Do not give CIPRO to anyone other than the person for which it was prescribed.
- This information does not take the place of discussions with your doctor or health care professional about your medication or treatment.

Rx Only
PX###### 6/01 Bay o 9867 5202-2-A-U.S.-10 © 2001 Bayer Corporation XXXX
CIPRO® (ciprofloxacin) 5% and 10% Oral Suspension Made in Italy. Printed in U.S.A.

Cipro IV Label
The approved package insert for NDA 19-847 (IV in vials) and NDA 19-857 (IV in 5% dextrose) dated August, 2000 was electronically compared to the proposed draft labeling dated June 29, 2001, received July 2, 2001. The changes were as follows:

1. **DESCRIPTION**
"Latex-free" was added to the following sentence to read:

> "The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride."

2. CLINICAL PHARMACOLOGY

•As we requested, new subheadings were added to this section and existing information was reorganized under the following; **Absorption, Distribution, Metabolism, Excretion** and **Special Populations**.

•The following paragraph concerning probenecid was deleted since the same information is stated in **Drug Interactions:**

•The following paragraph was added to read:

> **"Drug-drug Interactions:** The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **PRECAUTIONS: Drug Interactions.**)"

•The **Microbiology** subsection was revised as follows:

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

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.

Moved from lines 274-277 pursuant to Peter Dionne's comments dated 6/29/00

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) 5% and 10% Oral Suspension.

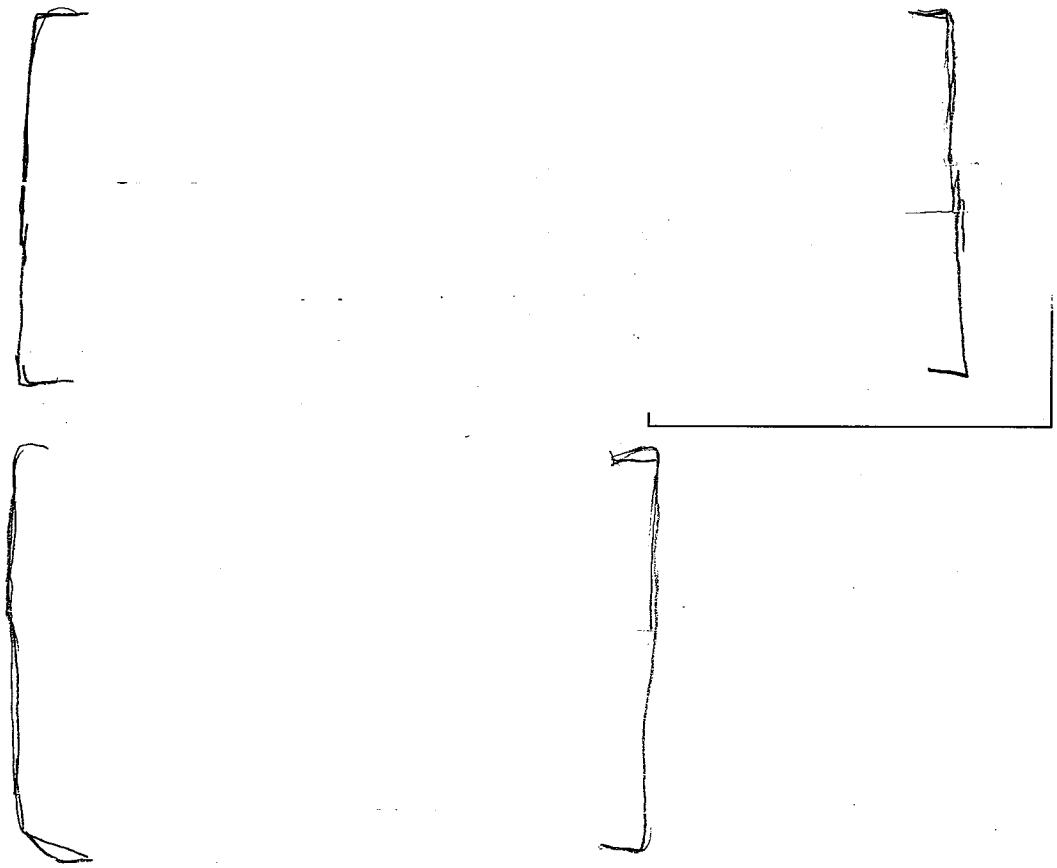
Pursuant to Peter Dionne's comments dated 6/29/00

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Citrobacter diversus	*Morganella morganii*
Citrobacter freundii	*Proteus mirabilis*
Enterobacter cloacae	*Proteus vulgaris*
Escherichia coli	*Providencia rettgeri*
Haemophilus influenzae	*Providencia stuartii*

Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Pseudomonas aeruginosa
Serratia marcescens



Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

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 ciprofloxacin intravenous formulations in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

New text to clarify I.V. formulation

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains)

Pursuant to the FDA's comments dated 6/29/00 and 3/5/01 regarding the Tablet PI. Also, added organisms from the tablet PI that are not included in the first list of the I.V. PI

Aerobic gram-negative microorganisms

Acinetobacter Iwoffii
Aeromonas hydrophila
Campylobacter jejuni
Edwardsiella tarda
Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Neisseria gonorrhoeae
Pasteurella multocida
Salmonella enteritidis
Salmonella typhi
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

[ ]

Moved to lines 162-164 and 159-160 pursuant to Peter Dionne's comments dated 6/29/00 regarding the tablet PI

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 aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*,

[ ]

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

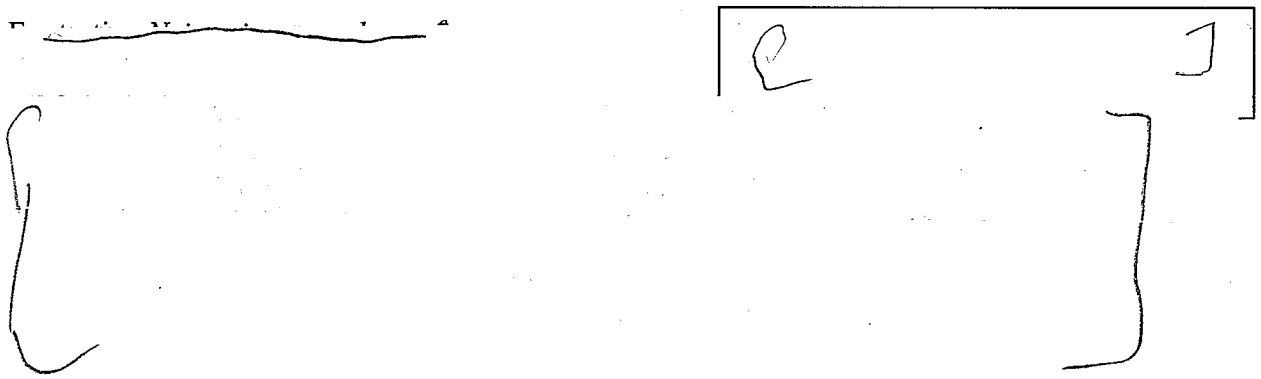
[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

MIC (µg/mL)	**Interpretation**
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible " category should be submitted to a reference laboratory for further testing.



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

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

Organism		**MIC (µg/mL)**
E. faecalis	ATCC 29212	0.25-2.0
E. coli	ATCC 25922	0.004-0.015
H. influenzae[a]	ATCC 49247	0.004-0.03
P. aeruginosa	ATCC 27853	0.25-1.0
S. aureus	ATCC 29213	0.12-0.5

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]

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 aerobic microorganisms other than *Haemophilus influenzae,* and *Haemophilus parainfluenzae,*-

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

[a]These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	Interpretation
≥ 21	Susceptible (S)

[b]This zone diameter standard is applicable only to tests *with Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

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omments
dated 6/29/00
regarding the
Tablet PI

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

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

Organism		Zone Diameter (mm)
E. coli	ATCC 25922	30-40
H. influenzae[a]	ATCC 49247	34-42
P. aeruginosa	ATCC 27853	25-33
S. aureus	ATCC 25923	22-30

[a]These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)[2].

3. **INDICATIONS AND USAGE**

•The **Lower Respiratory Infections** statement was revised to read:

> **"Lower Respiratory Infections** caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae or Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis."

Added to be consistent with tablet PI

•The references to **DOSAGE AND ADMINISTRATION** in the **Complicated intra-Abdominal Infections** and **Empirical Therapy for Febrile Neutropenic Patients** statements were deleted since this reference appears at the beginning of this section.

4. **CLINICAL STUDIES**

•The following demographic information for **Empirical Therapy for Febrile Neutropenic Patients** was deleted for brevity:

5. **PRECAUTIONS**

•The **Information for Patients** subsection was revised to read:

Information For Patients: Patients should be advised:

- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

- that ciprofloxacin may cause dizziness and lightheadedness;

- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.

- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

•The following two statements were moved from the **CLINICAL PHARMACOLOGY** section and added to the **Drug Interactions** subsection:

"The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly."

"Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 µg/mL ½ hour and 1.18 µg/mL between 6-8 hours after the end of infusion."

•At the end of the **Drug Interactions** subsection the following statement was deleted to be consistent with other quinolone labeling. It is also not a drug interaction:

[redacted]

6. ADVERSE REACTIONS

•The following sentence was moved up to the first paragraph and is now the last sentence in that paragraph:

> "Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment."

•The following events were moved to the third paragraph to the "additional events" table for consistency:

Include events from lines 860-861 into the table for consistency

"HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time"

"MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis"

•The following post-marketing adverse events were changed from table format to paragraph format to be consistent with other quinolone labeling and for brevity as follows:

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:
change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of seru triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tedinitis/tend rupture, vaginal candidiasis (See PRECAUTIONS.)

Revised to be consistent with other quinolone labeling and to help shorten the PI. No events have been deleted.

[redacted]

7. DOSAGE AND ADMINISTRATION

•This section was completely revised as follows:

CIPRO I.V. should be administered by intravenous infusion over a period of 60 minutes at dosages described in the Dosage Guidelines table. Slow infusion of a dilute solution into a larger vein will minimize patient discomfort and reduce the risk of venous irritation. (See Preparation of CIPRO I.V. for Administration section.)

Added a Usual Duration column to table below therefore text is redundant

Moved to lines 978-982

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative microorganism, the integrity of the patient's host-defense mechanisms, and the status of renal and hepatic function.

Added Usual Duration Column to table and removed Daily Dose column

DOSAGE GUIDELINES

Intravenous

Infection†	Type or Severity	Unit Dose	Frequency	Usual Duration
Urinary Tract	Mild/Moderate	200 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q12h	7-14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Nosocomial Pneumonia	Mild/Moderate/ Severe	400 mg	q8h	10-14 Days
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4-6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4-6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7-14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe			
	Ciprofloxacin +	400 mg	q8h	7-14 Days
	Piperacillin	50 mg/kg Not to exceed 24 g/day	q4h	
Inhalational anthrax (post-exposure)**	Adult	400 mg	q12h	60 Days
	Pediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q12h	60 Days

Added to be consistent between oral and I.V. PIs regarding Anthrax

* used in conjunction with metronidazole. (See product labeling for prescribing information.)
†DUE TO THE DESIGNATED PATHOGENS (See INDICATIONS AND USAGE.)
** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

CIPRO® I.V. should be administered by intravenous infusion over a period of 60 minutes.

Moved from lines 984-985

(CIPRO® Tablets and CIPRO – Oral Suspension) for oral administration are available. Parenteral therapy may be switched to oral CIPRO when the condition warrants, at the discretion of the physician.

See CLINICAL PHARMACOLOGY, and table below for the equivalent dosing regimens.)

Moved from lines 990-993 and included minor text revisions

Pursuant to 3/5/01 FDA comments

Equivalent AUC Dosing Regimens

CIPRO Oral Dosage	Equivalent CIPRO I.V. Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

Moved to lines 966-967

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Impaired Renal Function: The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	**Dosage**

>30	See usual dosage.
5-29	200-400 mg q 18-24 hr

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance:

Men: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

Preparation of CIPRO I.V. for Administration New text

Vials (Injection Concentrate): THIS PREPARATION MUST BE DILUTED BEFORE USE. The intravenous dose should be prepared by aseptically withdrawing the concentrate from the vial of CIPRO® I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1-2mg/mL. (See **COMPATIBILITY AND STABILITY**.) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of CIPRO I.V. If the concomitant use of CIPRO I.V. and another drug is necessary, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Moved up from lines 1059-1061. Revised wording

Flexible Containers: CIPRO I.V. is also available as a 0.2% premixed solution in 5% dextrose in flexible containers of 100 mL or 200 mL. The solutions in flexible containers do not need to be diluted and may be infused as described above.

COMPATIBILITY AND STABILITY

Ciprofloxacin injection 1% (10 mg/mL), when diluted with the following intravenous solutions to concentrations of 0.5 to 2.0 mg/mL, is stable for up to 14 days at refrigerated or room temperature storage.

0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
Sterile Water for Injection
10% Dextrose for Injection
5% Dextrose and 0.225% Sodium Chloride for Injection
5% Dextrose and 0.45% Sodium Chloride for Injection
Lactated Ringer's for Injection

Moved to lines 1037-1040

8. HOW SUPPLIED

•The second and third sentences in the first paragraph were revised to read:

"The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:
VIAL: manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220."

On November 14, 2001, an internal team meeting was held with Nancy Ostrove in DDMAC to discuss her proposed Patient Package Insert (PPI) for Cipro Tablets and Oral Solution (as requested by Dr. Sandy Kweder in response to the Anthrax crisis in the USA) and the PPI proposed by Bayer in June, 2001. It was decided that Dr. Eileen Navarro, Medical Officer would mesh the two proposed PPIs and draft an FDA response to Bayer. Once Dr. Rigo Roca, Medical Team Leader and Dr. Renata Albrecht, Acting Division Director concurred, the proposed FDA revisions would be faxed to Bayer. A fax with the following FDA revised PPI was sent to Bayer on January 14, 2002:

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. [redacted] doctor has prescribed CIPRO [redacted]. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO is right for you.

What is CIPRO?
CIPRO is an antibiotic. [redacted]

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?
CIPRO Tablets:
Unless directed otherwise by your physician, CIPRO should be taken twice a day, at approximately the same time, in the morning and in the evening.

CIPRO Oral Suspension:
Take CIPRO Oral Suspension in the same way as above. In addition, remember to shake the bottle vigorously each time before use for approximately 15 seconds to make sure the suspension is mixed well. Be sure to swallow the required amount of suspension.

Who should not take CIPRO?
You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones".

CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant, or plan to become pregnant while taking CIPRO,

In general, CIPRO is not recommended

What are the possible side effects of Cipro?

Cipro is generally well tolerated. The most common side effects caused by CIPRO, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort.

. If you develop hives, difficulty breathing, or other symptoms of an allergic

reaction, [redacted]. If you develop a skin rash, you should stop taking CIPRO and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPRO.

CIPRO has been rarely associated with inflammation of tendons. If you have pain, swelling or rupture of a tendon, you should stop taking CIPRO and call your health care professional.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

[redacted]

Cipro can affect how other medicines work. Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline or [redacted]

Remember:

Do not give CIPRO to anyone other than the person for [redacted] it was prescribed.

Take your dose of CIPRO in the morning and in the evening.

Complete the course of CIPRO even if you are feeling better.

Keep CIPRO and all medications out of reach of children.

[redacted]

On December 18, 2001 an internal team meeting was held with Dr. Kathleen Uhl, Medical Officer, CDER Pregnancy Labeling Team, to discuss revised pregnancy labeling for Cipro. Bayer had been informed in November, 2001 that the Agency would like to strengthen the current pregnancy labeling and would be forwarding proposed labeling revisions in the near future. In addition, the company was notified of two other comments from Dr. Navarro and Dr. Roca concerning Cipro labeling. A fax with the following proposed labeling revisions was sent to Bayer on December 19, 2001:

1. **PRECAUTIONS, Information for Patients**

[redacted]

"Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption."

2. **PRECAUTIONS**

Please replace the current wording with the following:

Pregnancy: Teratogenic Effects. Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women.

An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.

Robin Anderson, RN, MBA
Regulatory Review Officer

Eileen Navarro, MD
Medical Officer

cc:
HFD-590/ActingDivDir/R. Albrecht
HFD-590/MedTL/R. Roca
HFD-590/MO/E. Navarro
HFD-590/D. Matecka
HFD-590/Micro/P. Dionne
HFD-590/PM/J. Saliba
K. Uhl/MO CDER Pregnancy Labeling Team

Concurrence:
HFD-590/ActingDivDir/R. Albrecht 1/30/01
HFD-590/MedTL/R. Roca 1/30/02
HFD-590/MO/E. Navarro 1/30/02

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

/s/

Robin Anderson
1/31/02 08:49:08 AM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 1/30/02.

Renata Albrecht
1/31/02 03:33:27 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

NDA 19-537/S-041, NDA 20-780/S-011
NDA 19-847/S-026, NDA 19-857/S-028, NDA 19-858/S-022

Labeling, Clinical and Chemistry Review #2 of Supplemental Labeling Revisions (SLRs)
Review of Bayer's Response to January 31, 2002 Approvable Letters:

Amendments Reviewed:

Product	NDA #	SLR #	Letter Date	Receipt Date	Completed Date
CIPRO® (ciprofloxacin) Tablets, 100 mg, 250 mg, 500 mg, 750 mg	19-537	041	February 28, 2002 April 1, 2002	March 1, 2002 April 2, 2002	April 12, 2002
CIPRO® (ciprofloxacin) Oral Suspension, 5% and 10%, 250 mg, 500 mg	20-780	011	February 28, 2002 April 1, 2002	March 1, 2002 April 2, 2002	April 12, 2002
CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg	19-847	026	February 28, 2002 March 27, 2002	March 1, 2002 March 28, 2002	April 12, 2002
CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg	19-857	028	February 28, 2002 March 27, 2002	March 1, 2002 March 28, 2002	April 12, 2002
CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg (never launched)	19-858	022	February 28, 2002 March 27, 2002	March 1, 2002 March 28, 2002	April 12, 2002

- FDA approvable letter for NDA 19-537/S-041 and NDA 20-780/S-011 dated January 31, 2002
- FDA approvable letter for NDA 19-847/S-026, NDA 19-857/S-028 and NDA 19-858/S-022 dated January 31, 2002
- FDA fax to Bayer with labeling comments for February 28, 2002 submission dated March 21, 2002

Sponsor: Bayer Corporation Pharmaceutical Division

Background:
In December 2000/January 2001 Bayer submitted the labeling supplements noted above for prior approval (see Labeling and Clinical Review of these supplemental applications dated January 31, 2002). These SLRs provided for multiple changes to the Cipro package inserts in order to be more consistent with current labeling standards. The length was shortened to "make the package insert more physician friendly while maintaining all pertinent and required information." Microbiology labeling changes proposed by Peter Dionne, Microbiology Reviewer and faxed to the company on June 29, 2000 were also included in these submissions. A new Patient Information section (PPI) was also added to the Cipro oral formulation label. During labeling negotiations, FDA also recommended updated pregnancy labeling revisions.

On January 31, 2002, two approvable letters were sent to Bayer for the labeling supplements noted above (one for the Cipro oral label and one for the Cipro IV label). Bayer responded with a counterproposal for pregnancy labeling and the patient package insert (PPI) in an amendment submitted to the Cipro NDAs on February 28, 2002, received March 1, 2002.

On March 19, 2002 the FDA Cipro review team met to discuss the February 28, 2002 submission. The following comments were faxed to Bayer on March 21, 2002:

CIPRO Tablets and CIPRO IV Labels

•In the **DESCRIPTION** section, please revise the USP statement to read:

Does not comply with USP~~.~~ with regards to "loss on drying" and "residue on ignition".

Note: Exceptions must be explicitly listed.

•In the **PRECAUTIONS** section, **Pregnancy** subsection, please delete the words '[redacted]' in the following sentence:

[redacted]

Note: The endpoint '[redacted]' is poorly defined and it is a term that ACOG recommends not be used. Its appearance in the summary/labeling is misleading.

CIPRO Tablet Label Only

•In the **CLINICAL STUDIES** section, we agree that the sinusitis study may be removed, but please keep the UTI study information. The information that this section communicates is important in helping physicians to make a dosage regimen selection.

A revised label incorporating the FDA comments noted above was sent to the Division on March 27, 2002 for Cipro IV label and April 1, 2002 for Cipro oral label. The UTI study wording for the Cipro oral label had been negotiated via e mail with Andrew Verderame at Bayer on March 27, 2002, and the wording that the Division recommended was included in the revised label.

Electronic Labeling Comparison

Cipro Oral Formulation:

The last approved label dated August 30, 2000 was electronically compared to the proposed draft label dated April 1, 2002. The changes were as follows:

Double underline=added
~~Strikethrough~~=deleted

1. **DESCRIPTION**

•The description of tablet color and the addition of "corn" to the word "starch" were added as follows:

Ciprofloxacin tablets are white to slightly yellowish. CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

•The following sentence was added to the end of this section to read:

"* Does not comply with USP with regards to "loss on drying" and "residue on ignition."

2. **CLINICAL PHARMACOLOGY**

•As we requested, new subheadings were added to this section and existing information was reorganized under the following; **Absorption, Distribution, Metabolism, Excretion** and **Special Populations**.

•Under **Absorption**, the following sentence was added and is now the third sentence in the second paragraph:

The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

•The **Microbiology** subsection was revised as follows:

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

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

[ ]

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO ~ (ciprofloxacin hydrochloride) Tablets and CIPRO ~ (ciprofloxacin) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni	*Proteus mirabilis*
Citrobacter diversus	*Proteus vulgaris*
Citrobacter freundii	*Providencia rettgeri*
Enterobacter cloacae	*Providencia stuartii*
Escherichia coli	*Pseudomonas aeruginosa*
Haemophilus influenzae	*Salmonella typhi*
Haemophilus parainfluenzae	*Serratia marcescens*
Klebsiella pneumoniae	*Shigella boydii*
Moraxella catarrhalis	*Shigella dysenteriae*
Morganella morganii	*Shigella flexneri*
Neisseria gonorrhoeae	*Shigella sonnei*

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

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 ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains only)

Aerobic gram-negative microorganisms

Acinetobacter Iwoffii	*Pasteurella multocida*
Aeromonas hydrophila	*Salmonella enteritidis*
Edwardsiella tarda	*Vibrio cholerae*
Enterobacter aerogenes	*Vibrio parahaemolyticus*
Klebsiella oxytoca	*Vibrio vulnificus*
Legionella pneumophila	*Yersinia enterocolitica*

Reviewer Note: "Acinetobacter Iwoffi" is spelled incorrectly in the list above. There should be one i, not two.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

[redacted]

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 aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

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

[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible " category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*[c]:

MIC (µg/mL)	Interpretation
≤ 0.06	Susceptible (S)
0.12 – 0.5	Intermediate (I)
≥ 1	Resistant (R)

[c] This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

[redacted]

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

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

Organism		MIC (µg/mL)
E. faecalis	ATCC 29212	0.25-2.0
E. coli	ATCC 25922	0.004-0.015
[illegible]	[illegible]	0.001-0.008
P. aeruginosa	ATCC 27853	0.25-1.0
S. aureus	ATCC 29213	0.12-0.5

[a]This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]

[b]This quality control range is applicable to only [redacted] *ie* ATCC 49226 tested by an agar dilution procedure using GC agar base and 1% defined growth supplement.

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 aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

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

[a]These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	Interpretation
=21	Susceptible (S)

[b]This zone diameter standard is applicable only to tests *with Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing [redacted]

Zone Diameter (mm)	Interpretation
~~≥36~~ 41	Susceptible (S)
28 – 40	Intermediate (I)
≤ 27	Resistant (R)

[c]This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin. As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Organism		Zone Diameter (mm)
E. coli	ATCC 25922	30-40
H. influenzae[a]	ATCC 49247	34-42
[redacted]	ATCC 49226	48-58
P. aeruginosa	ATCC 27853	25-33
S. aureus	ATCC 25923	22-30

[a] These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM).[2]

[b] These quality control limits are applicable only to tests conducted with [redacted]*e* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

3. **INDICATIONS AND USAGE**

•As we requested, the order of the following indications was revised as follows:

[redacted]

Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.* (See **DOSAGE AND ADMINSTRATION.**)

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*

Lower Respiratory Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

Acute Sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae,* or *Moraxella catarrhalis.*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused *by Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.* (See **DOSAGE AND ADMINSTRATION.)**

[redacted]

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii*, Shigella dysenteriae, Shigella - flexneri* or *Shigella sonnei** when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi.*

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae.*

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4] (See also, **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their

susceptibility to ciprofloxacin. Therapy with CIPRC– may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

4. **PRECAUTIONS**

•The first bullet under **Information for Patients** was revised to read:

> ♦that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours before or six hours after taking these products. Ciprofloxacin should not be taken dairy products (like milk or with yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced. However, ciprofloxacin may be taken with a meal that contains these products.

REVIEWER NOTE: *This wording was not previously discussed with Bayer, but in an e-mail message dated March 20, 2002, Dr. Joette Meyer, Biopharmacuetics Reviewer stated that she agreed with the Bayer's proposed wording.*

•The following paragraph was deleted in the **Drug Interactions** subsection to be consistent with other quinolone labeling:

[ ]

•The Pregnancy: Teratogenic Effects. Pregnancy Category C subsection was revised to read:

> There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]
>
> A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of

spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

•The following sentence was added to the **Nursing Mothers** subsection and is now the second sentence:

"The amount of ciprofloxacin absorbed by the nursing infant is unknown."

5. **ADVERSE REACTIONS**

•The first paragraph in this section was revised to read:

During clinical investigation with the tablet, 2,799 patients received 2,868 courses of the drug.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients treated,

•The following adverse events were added to this subsection:

BODY AS A WHOLE: foot pain

HEMIC/LYMPHATIC: lymphadenopathy

•The following sentence was deleted after the list of additional events:

[redacted]

•The following paragraph was deleted (was the fourth paragraph in this section):

[redacted]

•In the **Post-Marketing Adverse Events** subsection, the following paragraph was added to replace the table of adverse events that previously existed (to be consistent with other quinolone labeling):

agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, flatulence, glucose elevation (blood), hemolytic anemia, hepatic necrosis, hypotension (postural), jaundice, methemoglobinemia, myalgia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), vaginal candidiasis, and vasculitis (See **PRECAUTIONS**.)

6. **OVERDOSAGE**

•The following sentence was moved and is now the last sentence in this section:

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

7. **DOSAGE AND ADMINISTRATION**

•This section was completely revised and now reads:

CIPRO Tablets and Oral Suspension should be administered orally as described in the Dosage Guidelines table.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the

integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable / buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc.

DOSAGE GUIDELINES

Infection	Type or Severity	Unit Dose	Frequency	Usual Durations†
Urinary Tract	Acute Uncomplicated	100 mg or 250 mg	q 12 h	3 Days
	Mild/Moderate	250 mg	q 12 h	7 to 14 Days
	Severe/Complicated	500 mg	q 12 h	7 to 14 Days
Chronic Bacterial Prostatitis	Mild/Moderate	500 mg	q 12 h	28 Days
Lower Respiratory Tract	Mild/Moderate	500 mg	q 12 h	7 to 14 days
	Severe/Complicated	750 mg	q 12 h	7 to 14 days
Acute Sinusitis	Mild/Moderate	500 mg	q 12 h	10 days
Skin and Skin Structure	Mild/Moderate	500 mg	q 12 h	7 to 14 Days
	Severe/Complicated	750 mg	q 12 h	7 to 14 Days
Bone and Joint	Mild/Moderate	500 mg	q 12 h	≥ 4 to 6 weeks
	Severe/Complicated	750 mg	q 12 h	≥ 4 to 6 weeks
Intra-Abdominal*	Complicated	500 mg	q 12 h	7 to 14 Days
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q 12 h	5 to 7 Days
Typhoid Fever	Mild/Moderate	500 mg	q 12 h	10 Days
Urethral and Cervical Gonococcal Infections	Uncomplicated	250 mg	single dose	single dose
Inhalational anthrax (post-exposure)**	Adult	500 mg	q 12 h	60 Days
	Pediatric	15 mg/kg per dose, not to exceed 500 mg per dose	q 12 h	60 Days

* used in conjunction with metronidazole
† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).
** Drug administration should begin as soon as possible after suspected or confirmed exposure.
This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.**

Patients whose therapy is started with CIPRO I.V. may be switched to CIPRO Tablets or Oral Suspension when clinically indicated at the discretion of the physician (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens).

Equivalent AUC Dosing Regimens

Cipro Oral Dosage	Equivalent Cipro I.V Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

Impaired Renal Function: Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment:

A. RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	**Dose**
>50	See Usual Dosage.
30 - 50	250-500 mg q 12 h
5 - 29	250-500 mg q 18 h
Patients on hemodialysis or Peritoneal dialysis)	250-500 mg q 24 h (after dialysis)

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be administered at the intervals noted above; however, patients should be carefully monitored and the serum ciprofloxacin concentration should be measured periodically. Peak concentrations (1-2 hours after dosing) should generally range from 2 to 4 μg/mL.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

8. **HOW SUPPLIED**

•The paragraph and table concerning Cipro Oral Suspension were revised as follows:

CIPRO® Oral Suspension is supplied in 5% and 10% strengths. The drug product is composed of two components

(microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist. See Instructions To The Pharmacist For Use/Handling.

Strengths	Total volume after reconstitution	Ciprofloxacin Concentration	Ciprofloxacin contents per bottle	*NDC Code*
5%	100 mL	250 mg/5 mL	5,000 mg	0026-8551-36
10%	100 mL	500 mg/5 mL	10,000 mg	0026-8553-36

9. As we agreed, the original **CLINICAL STUDIES** section was deleted and replaced by the following:

Uncomplicated Cystitis

Two double-blind, controlled clinical studies of acute uncomplicated cystitis in women were performed in the U.S. At the 5-9 day post-therapy follow-up visit, the clinical resolution rates in the first study, which compared ciprofloxacin 100 mg BID for 3 days to ciprofloxacin 250 mg BID for 7 days, were 87% (82/94) and 94%, (81/86), respectively. For *E. coli*, the bacteriological eradication rates for the first study were 91% (64/70) in the ciprofloxacin 100 mg regimen and 97% (67/69) in the ciprofloxacin 250 mg regimen. The second study's bacteriological eradication rates were 95% (117/123) for the ciprofloxacin 100 mg regimen and 98% (103/105) for the control regimen. Pooled eradication rates for the ciprofloxacin 100 mg treatment arms were 100% (16/16) for *S. saprophyticus.*

10. **Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension**
•The following information was added to the beginning of this section:

CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g ciprofloxacin in 100 mL) strengths. The drug product is composed of two components (microcapsules and diluent) which must be combined prior to dispensing.

One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250-mg of ciprofloxacin.
One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500-mg of ciprofloxacin.

Appropriate Dosing Volumes of the Oral Suspensions:

Dose	5%	10%
250-mg	5 mL	2.5 mL
500-mg	10 mL	5 mL
750-mg	15 mL	7.5 mL

•The following sentences were added to this section:

CIPRO Oral Suspension should not be administered through feeding tubes due to its physical characteristics.

Instruct the patient to shake CIPRO Oral Suspension vigorously each time before use for approximately 15 seconds and not to chew the microcapsules.

•**Instructions To The Patient For Taking CIPRO ~ Oral Suspension** was deleted since a new patient package insert has been added to the end of this label.

11. **REFERENCES**
•The following references were added:

7. Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.

8. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6): 1336-1339.

9. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure . Evaluation of a case registry of the European network of teratology information services (ENTIS). Eur J Obstet Gynecol Reprod Biol. 1996;69:83-89.

12. A new section called **"PATIENT INFORMATION ABOUT CIPRO® (ciprofloxacin hydrochloride) TABLETS, CIPRO® (ciprofloxacin) ORAL SUSPENSION"** was added to read:

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. If you have any concerns about you condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO is right for you.

What is CIPRO?

CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung, sinus, bone, and skin infections caused by certain germs called bacteria. CIPRO kills many types of bacteria that can infect these areas of the body. CIPRO has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). CIPRO, like all other antibiotics, does not kill viruses. You should contact your doctor if your condition is not improving while taking CIPRO.

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:

Unless directed otherwise by your physician, CIPRO should be taken twice a day at approximately the same time, in the morning and in the evening. CIPRO can be taken with food or on an empty stomach. CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, CIPRO may be taken with a meal that contains these products.

You should take CIPRO for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection. Do not take a double dose of CIPRO even if you miss a dose by mistake.

CIPRO Oral Suspension:

Take CIPRO Oral Suspension in the same way as above. In addition, remember to **shake the bottle vigorously each time before use for approximately 15 seconds** to make sure the suspension is mixed well. Be sure to swallow the required amount of suspension. Do not chew the microcapsules. Close the bottle completely after use. The product can be used for 14 days when stored in a refrigerator or at room temperature. After treatment has been completed, any remaining suspension should be discared.

Who should not take CIPRO?

You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones".

CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO talk to your doctor before taking this medication.

In general, CIPRO is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO?

CIPRO is generally well tolerated. The most common side effects, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort. If diarrhea persists, call your health care professional.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including CIPRO, even after just one dose. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking CIPRO and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPRO.

You should be careful about driving or operating machinery until you are sure CIPRO is not causing dizziness. Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. Be sure to let your physician know if you have a history of convulsions. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

CIPRO has been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPRO and call your health care professional.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

CIPRO can affect how other medicines work. Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO.

Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO and may prevent it from working. Other medications such as sulcrafate and Videx® (didanosine) chewable/buffered tablets or pediatric powder may also stop CIPRO from working. You should take CIPRO either 2 hours before or 6 hours after taking these products.

What if I have been prescribed CIPRO for possible anthrax exposure?

CIPRO has been approved to reduce the chance of developing anthrax infection following exposure to the anthrax bacteria. In general, CIPRO is not recommended for children; however, it is approved for use in patients younger than 18 years old for anthrax exposure. If you are pregnant, or plan to become pregnant while taking CIPRO, you and your doctor should discuss if the benefits of taking CIPRO for anthrax outweigh the risks.

CIPRO is generally well tolerated. Side effects that may occur during treatment to prevent anthrax might be acceptable due to the seriousness of the disease. You and your doctor should discuss the risks of not taking your medicine against the risks of experiencing side effects.

CIPRO can cause dizziness, confusion, or other similar side effects in some people. Therefore, it is important to know how CIPRO affects you before driving a car or performing other activities that require you to be alert and coordinated such as operating machinery.

Your doctor has prescribed CIPRO only for you. Do not give it to other people. Do not use it for a condition for which it was not prescribed. You should take your CIPRO for as long as your doctor prescribes it; stopping CIPRO too early may result in failure to prevent anthrax.

Remember:

Do not give CIPRO to anyone other than the person for whom it was prescribed.

Take your dose of CIPRO in the morning and in the evening.

Complete the course of CIPRO even if you are feeling better.

Keep CIPRO and all medications out of reach of children.

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

Rx Only

PX###### 3/02 Bay o 9867 5202-2-A-U.S.-10 © 2002 Bayer Corporation XXXX

CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy. Printed in U.S.A.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition".

Cipro IV Formulation:

The last approved label dated August 30, 2000 was electronically compared to the proposed draft label dated March 27, 2002. The changes were as follows:

Double underline=added
~~Strikethrough~~=deleted

1. **DESCRIPTION**

•The following sentence was deleted from the second paragraph in this section:

•"Latex-free" was added to the following sentence to read:

"The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride."

2. **CLINICAL PHARMACOLOGY**

•As we requested, new subheadings were added to this section and existing information was reorganized under the following; **Absorption, Distribution, Metabolism, Excretion** and **Special Populations**.

•The following paragraph concerning probenecid was deleted since the same information is stated in **Drug Interactions:**

•The following paragraph was added to read:

"**Drug-drug Interactions:** The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)"

•The **Microbiology** subsection was revised as follows:

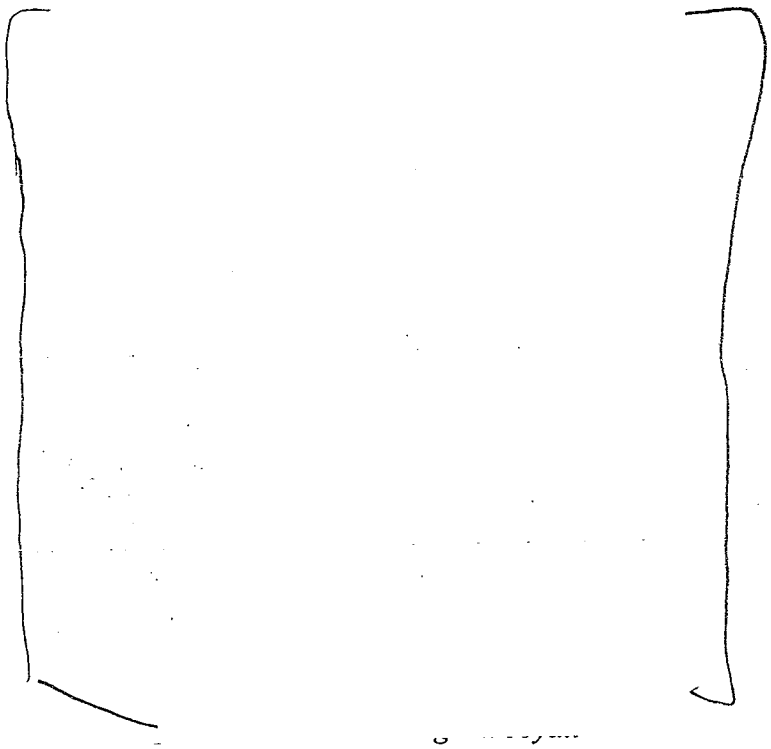
Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which ~~is~~ are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

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

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens



[ ]

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

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 ciprofloxacin intravenous formulations in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic gram-negative microorganisms
Acinetobacter Iwoffii
Aeromonas hydrophila
Campylobacter jejuni
Edwardsiella tarda
Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Neisseria gonorrhoeae
Pasteurella multocida
Salmonella enteritidis
Salmonella typhi
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Reviewer Note: "Acinetobacter Iwoffi" is spelled incorrectly in the list above. There should be one i, not two.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

[ ]

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 aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*,

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

[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible " category should be submitted to a reference laboratory for further testing.

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

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

Organism		**MIC (µg/mL)**
E. faecalis	ATCC 29212	0.25-2.0
E. coli	ATCC 25922	0.004-0.015
H. influenzae[a]	ATCC 49247	0.004-0.03
P. aeruginosa	ATCC 27853	0.25-1.0
S. aureus	ATCC 29213	0.12-0.5

[a]This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]

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 aerobic microorganisms other than *Haemophilus influenzae,* and *Haemophilus parainfluenzae,*-

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

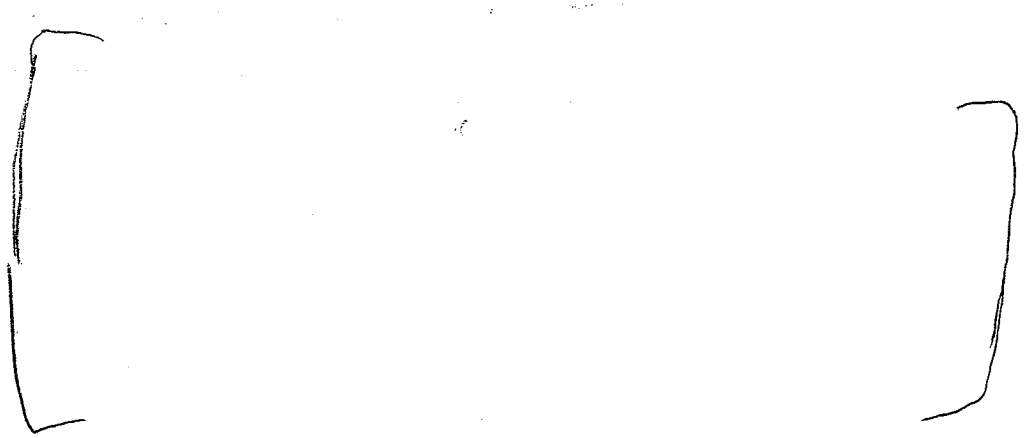
[a]These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	Interpretation
≤21	Susceptible (S)

[b]This zone diameter standard is applicable only to tests *with Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.



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

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

Organism		Zone Diameter (mm)
E. coli	ATCC 25922	30-40
H. influenzae[a]	ATCC 49247	34-42
P. aeruginosa	ATCC 27853	25-33
S. aureus	ATCC 25923	22-30

[a]These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)[2].

[redacted]

3. **INDICATIONS AND USAGE**

•The **Lower Respiratory Infections** statement was revised to read:

> **"Lower Respiratory Infections** caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, or Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis."

•The references to **DOSAGE AND ADMINISTRATION** in the **Complicated intra-Abdominal Infections** and **Empirical Therapy for Febrile Neutropenic Patients** statements were deleted since this reference appears at the beginning of this section.

4. **CLINICAL STUDIES**

•The following demographics information for **Empirical Therapy for Febrile Neutropenic Patients** was deleted for brevity:

[redacted]

5. **WARNINGS**

•There is a typographical error in the word "have" in the following statement that should be noted as a minor editorial correction in the approval letter:

> **THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), - EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED.** (See **PRECAUTIONS: Pediatric Use, Pregnancy**, and **Nursing Mothers** subsections.)

6. **PRECAUTIONS**

•The **Information for Patients** subsection was revised to read:

Information For Patients: Patients should be advised:

- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- that ciprofloxacin may cause dizziness and lightheadedness;
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

•The following two statements were moved from the **CLINICAL PHARMACOLOGY** section and added to the **Drug Interactions** subsection:

"The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly."

"Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 µg/mL ½ hour and 1.18 µg/mL between 6-8 hours after the end of infusion."

•At the end of the **Drug Interactions** subsection the following statement was deleted to be consistent with other quinolone labeling. It is also not a drug interaction:

•The Pregnancy: Teratogenic Effects. Pregnancy Category C subsection was revised to read:

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones-(52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses [redacted] up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. [redacted]

•The following sentence was added to the **Nursing Mothers** subsection and is now the second sentence:

"The amount of ciprofloxacin absorbed by the nursing infant is unknown."

7. ADVERSE REACTIONS

•The following sentence was moved and is now the last sentence in the first paragraph:

" Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment."

•The following events were moved from the third paragraph to the "additional events" table for consistency:

"HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time"

"MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis"

•The following post-marketing adverse events were changed from table format to paragraph format to be consistent with other quinolone labeling and for brevity as follows:

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:
change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of serum triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tedonitis/tendon rupture, vaginal candidiasis (See **PRECAUTIONS.)**

8. DOSAGE AND ADMINISTRATION

•This section was completely revised. The new text reads as follows:

CIPRO® I.V. should be administered by intravenous infusion over a period of 60 minutes at dosages described in the Dosage Guidelines table. Slow infusion of a dilute solution into a larger vein will minimize patient discomfort and reduce the risk of venous irritation. (See Preparation of CIPRO I.V. for Administration section.)

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative microorganism, the integrity of the patient's host-defense mechanisms, and the status of renal and hepatic function.

DOSAGE GUIDELINES

Intravenous

Infection†	Type or Severity	Unit Dose	Frequency	Usual Duration
Urinary Tract	Mild/Moderate	200 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q12h	7-14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10-14 Days
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4-6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4-6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7-14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin	400 mg 50 mg/kg Not to exceed 24 g/day	q8h q4h	7-14 Days
Inhalational anthrax (post-exposure)**	Adult	400 mg	q12h	60 Days
	Pediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q12h	60 Days

* used in conjunction with metronidazole. (See product labeling for prescribing information.)

†DUE TO THE DESIGNATED PATHOGENS (See **INDICATIONS AND USAGE.**)

** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.** Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

CIPRO I.V. should be administered by intravenous infusion over a period of 60 minutes.

CIPRO Tablets and CIPRO Oral Suspension for oral administration are available. Parenteral therapy may be switched to oral CIPRO when the condition warrants, at the discretion of the physician. (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens.)

Equivalent AUC Dosing Regimens	
CIPRO Oral Dosage	Equivalent CIPRO I.V. Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Impaired Renal Function: The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dosage
>30	See usual dosage.
5-29	200-400 mg q 18-24 hr

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance:

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

Preparation of CIPRO I.V. for Administration

Vials (Injection Concentrate): THIS PREPARATION MUST BE DILUTED BEFORE USE. The intravenous dose should be prepared by aseptically withdrawing the concentrate from the vial of CIPRO I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1-2mg/mL. (See **COMPATIBILITY AND STABILITY.**) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of CIPRO I.V. If the concomitant use of CIPRO I.V. and another drug is necessary each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Flexible Containers: CIPRO I.V. is also available as a 0.2% premixed solution in 5% dextrose in flexible containers of 100 mL or 200 mL. The solutions in flexible containers do not need to be diluted and may be infused as described above.

COMPATIBILITY AND STABILITY
Ciprofloxacin injection 1% (10 mg/mL), when diluted with the following intravenous solutions to concentrations of 0.5 to 2.0 mg/mL, is stable for up to 14 days at refrigerated or room temperature storage.

0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
Sterile Water for Injection
10% Dextrose for Injection
5% Dextrose and 0.225% Sodium Chloride for Injection
5% Dextrose and 0.45% Sodium Chloride for Injection
Lactated Ringer's for Injection

9. **HOW SUPPLIED**
•The third and fourth sentences in the first paragraph were revised to read:

"The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:
VIAL: manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220."

10. **STORAGE**
•The following USP statement was added to the end of this section:

"Ciprofloxacin is also available as CIPRO (ciprofloxacin HCl) Tablets 100, 250, 500, and 750 mg and CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition".

10. **REFERENCES**
The following references were added:

7. Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.

8. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6): 1336-1339.

9. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure . Evaluation of a case registry of the European network of teratology information services (ENTIS). Eur J Obstet Gynecol Reprod Biol. 1996;69:83-89.

APPEARS THIS WAY
ON ORIGINAL

Conclusions/Recommendations:
The labeling changes proposed by Bayer are acceptable. Two approval letters (one for Cipro Tablets/Oral Suspension and one for the CIPRO IV formulations) should be sent advising the applicant that these NDA labeling supplements are approved. The Cipro Tablet/Oral Solution letter should include the minor editorial correction noted in the patient package insert. The Cipro IV approval letter should include the minor editorial correction noted in **WARNINGS.**

Robin Anderson, R.N., M.B.A.
Regulatory Review Officer

Eileen Navarro, M.D.
Medical Officer

Dorota Matecka, Ph.D.
Chemistry Reviewer

cc:
HFD-590/ActingDivDir/R. Albrecht
HFD-590/MedTL/R. Roca
HFD-590/MO/E. Navarro
HFD-590/Chem/D. Matecka
HFD-590/ChemTL/N. Schmuff
HFD-590/Biopharm/J. Meyer
HFD-590/BiophramTL/B.Davit
HFD-590/Micro/P. Dionne
HFD-590/ MicroTL/S. Bala
HFD-590/PM/J. Saliba

Concurrence:
HFD-590/ActingDivDir/R. Albrecht 4/17/02
HFD-590/MedTL/R. Roca 4/17/02
HFD-590/MO/E. Navarro 4/16/02
HFD-590/Chem/D. Matecka 4/17/02
HFD-590/ChemTL/N. Schmuff 4/16/02
HFD-590/Biopharm/J. Meyer 4/16/02
HFD-590/BiophramTL/B.Davit 4/16/02
HFD-590/Micro/P. Dionne 4/16/02
HFD-590/ MicroTL/S. Bala 4/16/02

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

/s/

Robin Anderson
4/17/02 11:29:02 AM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 4/17/02.

Renata Albrecht
4/17/02 05:09:19 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-847/ S-026
19-857 / S-028
19-858 / S-022

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW

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

NDAs #: 19-847/SLR-026	**REVIEWER:**	Peter A. Dionne
19-857/SLR-028	**CORRESPONDENCE DATE:**	11-JAN-01
19-858/SLR-027	**CDER DATE:**	12-JAN-01
	REVIEW ASSIGN DATE:	18-JAN-01
	REVIEW COMPLETE DATE:	01-FEB-01

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

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

SUBMISSION REVIEWED: Labeling amendment—changes to Microbiology subsection

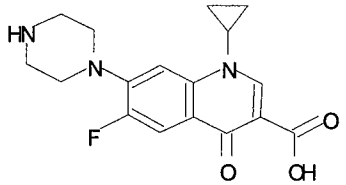
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Urinary Tract Infections, Prostatitis, Lower Respiratory Tract Infections, Nosocomial Pneumonia, Sinusitis, Skin and Skin Structure Infections, Bone and Joint Infections, Complicated Intra-Abdominal Infections, Infectious, Inhalational Anthrax (post-exposure)

DOSAGE FORM: I. V. solution—10 mg/mL: 2 mg/mL in 5% Dextrose; 2 mg/mL in 0.9% Saline

DRUG PRODUCT NAME

PROPRIETARY: CIPRO® I.V.
NONPROPRIETARY/USAN: ciprofloxacin
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: 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

BACKGROUND:

This is a labeling supplement. In this supplement the sponsor has revised the labeling for ciprofloxacin I.V. dosage forms to make the package insert more consistent with current labeling standards and to shorten the length of the label.

Bayer also acknowledges receipt of a facsimile dated June 29, 2000 regarding proposed revisions to the Microbiology subsection of the label. Bayer has incorporated the requested changes into this revision.

The following changes have been made to the Microbiology subsection of the labeling. Additions are indicated by a double-underline and deletions by a strikeout.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from ~~bitior~~ the enzymes topoisomerase II (DNA gyrase) and ~~IV, w... are required or t~~ acterial DNA replication, transcription, repair, and r~~on.~~ ~~i~~ of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillin, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms, resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. In vitro resistance to ciprofloxacin develops slowly by multiple step mutations.

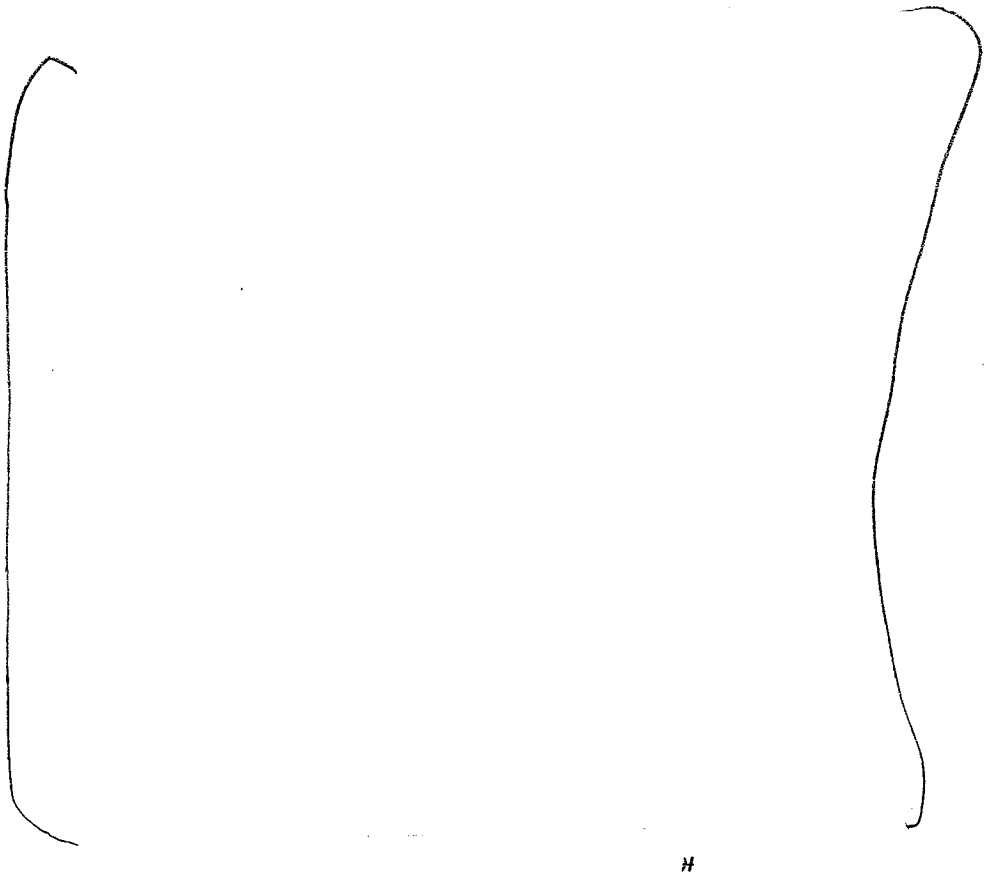
Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

***Reviewer's Comments*: These revisions were recommended to the sponsor in the June 29, 2000 facsimile and make the label more consistent with other quinolone labeling. Information about the activity being less when tested at acidic pH and about the MBC generally being 2 times the MIC has been moved from lines 230-234 to lines 143-145. Information about cross reactions with other classes of drugs has been moved from lines 236-238 to lines 139-141. These changes in the ciprofloxacin label will make it more consistent with other antibacterial labels.**

In line 140 the words " In vitro" should be in italics.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® I.V.(ciprofloxacin for intravenous infusion).

[ ]



Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICTIONS AND USAGE** and **INHALATIONAL ANTHRAX—ADDITIONAL INFORMATION).**

***Reviewer's Comments*: *Staphylococcus aureus* and *Staphylococcus epidermidis* in lines 154 and 155 should be qualified as (methicillin-susceptible strains only) instead of [illegible] *reptococcus pneumoniae* in line 157 should be qualified as (penicillin-susceptible strains) instead of [illegible]**

The deletion of the CIPRO® Tablet list of organisms appears to be acceptable. This will make the package insert shorter and may eliminate confusion since very few if any other labels have two clinical e[illegible]s. Most of the organisms are the same in both l[illegible] except for [illegible] and organisms associated with [illegible] and [illegible] which the I.V. formulation is not approved for. The CIPRO® I.V. label will have additional organisms added to the *in vitro* listing which will not be associated with infections for which the I.V. formulation is approved. This does not seem to be a real problem, however, since the oral formulations are approved for these organisms and the I.V. label already has *Vibrio* species and *Yersinia enterocolitica* included.

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 ciprofloxacin intravenous formulations in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae [illegible]

Aerobic gram-negative microorganisms

Acinetobacter lwoffi	*Salmonella typhi*
Aeromonas hydrophila	*Shigella boydii*
Campylobacter jejuni	*Shigella dysenteriae*
Edwardsiella tarda	*Shigella flexneri*
Enterobacter aerogenes	*Shigella sonnei*
Klebsiella oxytoca	*Vibrio cholerae*
Legionella pneumophila	*Vibrio parahaemolyticus*
Neisseria gonorrhoeae	*Vibrio vulnificus*
Pasteurella multocida	*Yersinia enterocolitica*
Salmonella enteritidis	

226 Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia*
227 are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides*
228 *fragilis* and *Clostridium difficile*.
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***Reviewer's Comments*: The addition of the words "intravenous formulations to line 205 is acceptable. This clarifies that the organisms in the lists that follow pertain only to the I.V. formulations. *Streptococcus pneumoniae* in line 210 should be qualified as (penicillin-resistant strains) instead of (The addition of the organisms to the Aerobic gram-negative microorganisms list is acceptable since the oral formulations have shown clinical efficacy against them. Although these organisms are not associated with infections approved for the I.V. formulation other organisms such as *Vibrio* species have been included. The deletion of the two paragraphs (lines 230-238) is acceptable since this information has been moved to the introduction of the Microbiology subsection (lines 138-145). The last paragraph (lines 240-243) has been deleted as requested in the June 29, 2000 facsimile.**

244
245 **Susceptibility Tests**

***Reviewer's Comments*: The only revisions to the Susceptibility Tests is the deletion of e Interpretive criteria and Quality Control information since the I.V. formulations are not approved for this organism. All these revisions are acceptable.**

CONCLUSIONS:

With a few minor revisions the changes made to the Microbiology subsection of the package insert are acceptable. These revisions are indicated below in the Recommendations section as notification to the sponsor.

RECOMMENDATIONS:

The sponsor should be notified of the following:

1. In line 140 the words In vitro should be in italic in the sentence that begins "In vitro resistance to ciprofloxacin develops slowly ...

2. *Staphylococcus aureus* and *Staphylococcus epidermidis* in lines 154 and 155 should be qualified as (methicillin-susceptible stains only) instead of (methicillin-susceptible).

3. *Streptococcus pneumoniae* in lines 157 and 212 should be qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the label instead of (penicillin-susceptible) and (penicillin-resistant)

All other revisions to the Microbiology subsection are acceptable.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:
HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA #19-847/SLR-026
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ENavarro
HFD-590/Chem/DMatecka
HFD-590/CSO/VJensen
HFD-590/CSO/RAnderson

/s/

Peter Dionne
2/21/01 09:16:51 AM
MICROBIOLOGIST

Shukal signed 2/1/2001 Ken signed 2/9/2001

Shukal Bala
2/21/01 10:26:34 AM
MICROBIOLOGIST

Kenneth Hastings
2/21/01 02:26:33 PM
PHARMACOLOGIST

MICROBIOLOGY REVIEW

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

NDAs #: 19-847/SLR-026	**REVIEWER:**	Peter A. Dionne
19-857/SLR-028	**CORRESPONDENCE DATE:**	29-JUN-01
19-858/SLR-022	**CDER DATE:**	02-JUL-01
	REVIEW ASSIGN DATE:	09-JUL-01
	REVIEW COMPLETE DATE:	11-JUL-01

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SUBMISSION REVIEWED: Labeling amendment—changes to Microbiology subsection

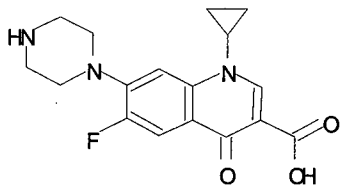
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Urinary Tract Infections, Lower Respiratory Tract Infections, Nosocomial Pneumonia, Skin and Skin Structure Infections, Bone and Joint Infections, Complicated Intra-Abdominal Infections, Acute Sinusitis, Chronic Bacterial Prostatitis, Empirical Therapy for Febrile Neutropenia, Inhalational Anthrax (post-exposure)

DOSAGE FORM: 200 mg and 400 mg vials (10 mg/mL); 100 mL and 200 mL Flexible Containers (2 mg/mL) in 5% Dextrose and 0.9% NaCl

DRUG PRODUCT NAME

PROPRIETARY: CIPRO® I.V.
NONPROPRIETARY/USAN: Ciprofloxacin
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: 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 #19-874—Bayer Ciprofloxacin IV 1%--Approved December 26, 1990
NDA #20-780—Bayer Ciprofloxacin Oral Suspension—Approved September 26, 1997
NDA #19-857—Bayer Ciprofloxacin IV in 5% Dextrose—Approved December 26, 1990
NDA #19-858—Bayer Ciprofloxacin IV in 0.9% NaCl—Approved December 26, 1990

BACKGROUND:

This is a labeling supplement. In this supplement the sponsor has revised the labeling for ciprofloxacin I.V. solutions to make the package insert more consistent with current labeling standards and to shorten the length of the label.

Bayer also acknowledges receipt of a facsimile dated March 5, 2001 that includes comments on these supplements that were submitted January 16, 2001. These submissions are Bayer's response to the Division's comments. Bayer has included a revised proposed label.

The microbiology comments and the sponsor's response to each are stated below.

1. In line 171 the words In vitro should be in italic in the sentence that begins "In vitro resistance to ciprofloxacin develops slowly ...

   The words "In vitro" have been italicized. Refer to line 159 in the revised proposed labeling.

2. *Staphylococcus aureus* and *Staphylococcus epidermidis* in lines 192 and 193 should be qualified as (methicillin-susceptible strains only) instead of

   Staphylococcus aureus and *Staphylococcus epidermidis* have been qualified as (methicillin-susceptible strains only). Refer to lines 173 and 174 in the revised proposed labeling.

3. *Streptococcus pneumoniae* in lines 195 and 249 should be qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the label instead of

   Streptococcus pneumoniae has been qualified as (penicillin-susceptible strains and (penicillin-resistant strains) in the appropriate sections of the revised label. Refer to lines 176 and 231 in the revised proposed labeling.

CONCLUSIONS:

The Microbiology subsection of the label is now acceptable.

RECOMMENDATIONS:

All revisions to the Microbiology subsection are acceptable.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:
HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA #19-847/SLR-026; NDA #19-857/SLR-028;
NDA #19-858/SLR-022
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ENavarro
HFD-590/Chem/DMatecka
HFD-590/Pharm/SHundley
HFD-590/CSO/JSaliba
HFD-590/CSO/RAnderson

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/s/

Peter Dionne
7/16/01 12:19:05 PM
MICROBIOLOGIST

shukal signed 7/12/01 Ken signed 7/16/01

Shukal Bala
7/16/01 12:37:51 PM
MICROBIOLOGIST

Kenneth Hastings
7/24/01 10:17:58 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-847/ S-026
19-857 / S-028
19-858 / S-022

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 19-857/SE1-028, 19-858/SE1-022, 19-847/SE1-026

Trade Name Cipro® **Generic Name** ciprofloxacin hydrochloride

Applicant Name Bayer **HFD-590**

Approval Date April 17, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

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

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/ **N/A**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/ **N/A**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_*X_/ NO /___/

*An efficacy supplement (NDA 19-537/SE1-016) was approved for the tablet formulation of Ciprofloxacin for the addition of *Moraxella catarrhalis* to the "Lower respiratory tract Infections" indication on 5/15/97. This was based on the review of new clinical studies conducted by the sponsor, for which 3 years of exclusivity was granted to the tablet but not the IV formulation. On April 17, 2002, changes to the label for the IV formulation to parallel the tablet formulation were approved, including the addition of *Moraxella catarrhalis* to the "Lower respiratory tract Infections" indication, based on the original clinical study data submitted to the tablet formulation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/ **N/A**

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES /___/ NO /___/ **N/A**

   (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/ **N/A**

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /_X_/	NO /___/
Investigation #2	YES /_X_/	NO /___/
Investigation #3	YES /_X_/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 19-537/SE1-016 Study # D84-028-01
NDA # 19-537/SE1-016 Study # D84-008-01
NDA # 19-537/SE1-016 Study # D84-051-01

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency,

or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

!
! _____
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Jouhayna Saliba
4/19/02 02:19:59 PM

Renata Albrecht
5/3/02 05:27:49 PM

NDA 19-847/S-026
NDA 19-857/S-028
NDA 19-858/S-022

Regulatory Review Officer Review of Final Printed Labeling (FPL)

Materials Reviewed:

Product	NDA #	FPL for SLR #	Letter Date	Receipt Date	Completed Date
CIPRO® (ciprofloxacin) I.V. in solution	19-847	026	August 7, 2002	August 8, 2002	August 16, 2002
CIPRO® (ciprofloxacin) I.V. in 5% dextrose	19-857	028	August 7, 2002	August 8, 2002	August 16, 2002
CIPRO® (ciprofloxacin) I.V. in 5% dextrose	19-858	022	August 7, 2002	August 8, 2002	August 16, 2002

•Approved draft labeling for NDA 19-847/S-026; NDA 19-857/S-028; NDA 19-858/S-022 dated April 17, 2002.

Applicant: Bayer Corporation

Background:
Supplements NDA 19-847/S-026, NDA 19-857/S-028, and NDA 19-858/ S-022 were prior approval supplements that provided for many changes to the CIPRO® IV package insert (see approval letter dated April 17, 2002 for a detailed listing of the changes). These supplements were approved on draft labeling with minor editorial revisions on April 17, 2002 and final printed labeling (FPL) was requested.

Review and Comments:
The FPL for the CIPRO® IV package insert submitted on August 7, 2002 was compared to the draft labeling for the CIPRO® IV package insert approved April 17, 2002. The following differences were found:

1. In the eighth sentence of the **DESCRIPTION** section [redacted] was changed to "1.0%" for accuracy. *This change is acceptable.*
2. In the fourth sentence of the **CLINICAL PHARMACOLOGY, Excretion** section, the word '[redacted]as changed to "than" to correct a typographical error. *This change is acceptable.*

3. The following sentences that had been inadvertently deleted from the **CLINICAL PHARMACOLOGY** section, **Excretion** subsection were reinserted.

> "Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (<1%) is recovered from the bile as unchanged drug. Approximately 15% of an I.V. dose is recovered from the feces within 5 days after dosing."

This revision was made as requested in the April 17, 2002 approval letter.

4. In the **CLINICAL PHARMACOLOGY** section, **Microbiology** subsection, 'Iwoffii" was replaced with "Iwoffi." *This revision was made as requested in the April 17, 2002 approval letter.*

5. In the first sentence of the WARNINGS section, "haven" was replaced with "have." *This revision was made as requested in the April 17, 2002 approval letter.*
6. Throughout the Package Insert "IV" was changed to "I.V." for consistency. *This change is acceptable.*

Recommendations:
An Acknowledge and Retain letter should be issued informing the applicant that the FPL for NDA 19-847/S-026, NDA 19-857/S-028, and NDA 19-858/S-022 is acceptable.

Susan Peacock, M.S.
Regulatory Project Manager,
HFD-590

cc:

Ellen C. Frank, R.Ph.
Chief, Project Management Staff,
HFD-590

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/s/

Susan Peacock
8/20/02 11:15:54 AM
CSO

I am slowly learning this system!

Ellen Frank
8/20/02 11:20:24 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-847/S-026
NDA 19-857/S-028
NDA 19-858/S-022

Bayer Corporation
Attention: Andrew Verderame
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Mr. Verderame:

We acknowledge receipt of your August 7, 2002, submission containing final printed labeling in response to our April 17, 2002, letter approving your supplemental new drug application for CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg; CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg; and CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg.

We have reviewed the labeling that you submitted in accordance with our April 17, 2002 letter and we find it acceptable.

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Marc Cavaille Coll
8/21/02 02:35:43 PM
For Renata Albrecht

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-847/S-026
NDA 19-857/S-028
NDA 19-858/S-022

PRIOR APPROVAL SUPPLEMENT

Bayer Corporation Pharmaceutical Division
Attention: Andrew S. Verderame
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
19-847	S-026	CIPRO (ciprofloxacin hydrochloride) I.V. vials
19-857	S-028	CIPRO (ciprofloxacin hydrochloride) I.V. flexibags in 5% Dextrose
19-858	S-022	CIPRO (ciprofloxacin) I.V. flexibags in 0.9% Saline

Date of Supplements: January 11, 2001

Date of Receipt: January 12, 2001

These supplemental applications, propose the following change**(s)**:

- Shorten the package insert
- Make the package insert more consistent

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on February 24, 2001 in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

NDA 19-847/S-026
NDA 19-857/S-028
NDA 19-858/S-022

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Valerie Jensen, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Ellen Frank
1/29/01 07:16:13 PM
NDA 19-847/S-026 & NDA 19-857/S-028 & NDA 19-858/S-022