CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-537 / S-025
19-847 / S-012
19-857 / S-013
19-858 / S-011

Trade Name: **Cipro**

Generic Name: **Ciprofloxacin**

Sponsor: **Bayer Corporation**

Approval Date: **September 26, 1997**

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 26 1997

NDA 19-537/S-025
NDA 19-847/S-012
NDA 19-857/S-013
NDA 19-858/S-011

SEP 26 1997

Ms. Ann Marie Assumma
Associate Director
Regulatory Affairs
Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Assumma:

Please refer to your, supplemental new drug applications (NDA's) dated March 24, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® (ciprofloxacin) Tablets, NDA 19-537/S-025, and CIPRO® I.V. (ciprofloxacin) For Intravenous Infusion, NDA's 19-847/S-012, NDA 19-857/S-013, and NDA 19-858/S-011.

We acknowledge receipt of your amendment dated September 24, 1996, and your facsimile dated September 25, 1997, in which you agreed to the proposed labeling changes.

These supplemental applications provide for revisions to the **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS** sections of the labeling.

We have completed our review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective as recommended in the draft labeling dated September 24, 1997, and amended in your facsimile dated September 25, 1997. Therefore, they are approved effective on the date of this letter.

The labeling revisions agreed to in your facsimile dated September 25, 1997, are are as follows:

WARNINGS
This new paragraph will replace the second paragraph of this section:

"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.**)"

PRECAUTIONS
General:

This new paragraph will be added and becomes the second paragraph of this subsection:

"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.**)"

ADVERSE REACTIONS

1) This new paragraph will be added and becomes the last paragraph in this section of the Oral ciprofloxacin labeling:

   "In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg BID) to cefuroxime axetil (250 mg - 500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs."

2) This new paragraph will be added and becomes the last paragraph in this section of the IV ciprofloxacin labeling:

These revisions are the terms of the supplemental NDA approval.

Please submit twenty-five copies of the FPL as soon as they are available, in no case 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 "FINAL PRINTED LABELING" for approved **NDA 19-537/S-025, NDA 19-847/S-012, NDA 19-857/S-013, NDA 19-858/S-011**. Approval of this submission by FDA is not required before the labeling is used.

cc: Original NDA 20-780 9/25/97
HFD-590/Div. files
HFD-590/Goldberger
HFD-590/Hopkins RLH 9/25/97
HFD-590/Coyne
HFD-590/Cavaille-Coll 9/25/97
HFD-590/Schmuff
DISTRICT OFFICE
HFD-2/M.Lumpkin
HF-2/Medwatch
HFD-40/DDMAC)
HFD-613
HFD-735
HFD-021/J.Treacy
drafted:Sept.24, 1997
final:9/25/97
APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537 / S-025
19-847 / S-012
19-857 / S-013
19-858 / S-011

LABELING

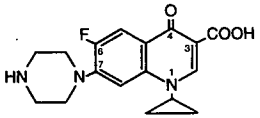
CIPRO® I.V.
(ciprofloxacin)
For Intravenous Infusion
PD500043 10/97

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

PD500043 10/97

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. 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. 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 1.0% 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 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

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. The serum elimination half-life is approximately 5–6 hours and the total clearance is around 35 L/hr. 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 C_{max} 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 q12h, 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] $AUC_{24h}=AUC_{0-12h} \times 2$
[c] $AUC_{24h}=AUC_{0-8h} \times 3$

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 than 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.

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

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. Although bile concentrations of ciprofloxacin are severalfold 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.

After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose.

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

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.

Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every 4 hours, mean serum ciprofloxacin concentrations were 3.02 μg/mL 1/2 hour and 1.18 μg/mL between 6–8 hours after the end of infusion.

The binding of ciprofloxacin to serum proteins is 20 to 40%.

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.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

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)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms

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

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.

Aerobic gram-positive microorganisms

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

Aerobic gram-negative microorganisms

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

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

Aerobic gram-negative microorganisms

Acinetobacter lwoffi
Aeromonas hydrophila
Edwardsiella tarda
Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Pasteurella multocida
Salmonella enteritidis
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.*

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro.* The minimum bactericidal concentration (MBC) generally does not exceed the minimum inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

In vitro studies have shown that additive activity often results when ciprofloxacin is combined with other antimicrobial agents such as beta-lactams, aminoglycosides, clindamycin, or metronidazole. Synergy has been reported particularly with the combination of ciprofloxacin and a beta-lactam; antagonism is observed only rarely.

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 tesing 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)

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

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 concen-

trated 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	
≥ 36	Susceptible	(S)

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

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 folowing 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.

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.*

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.* (See **DOSAGE AND ADMINISTRATION.**)

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

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.

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)

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 a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE 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 Interactions** 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.

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.

References: 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997. **2.** National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997. **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.

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

PD500043 10/97

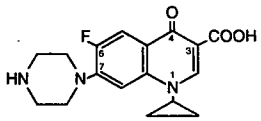
R 4 6 0

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

PD500043 10/97

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. Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at

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 ADMINISTERED 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.

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.

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.

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.

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.

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: Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/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 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 a an increased incidence of abortion, but no teratogenic was observed at either dose. After intravenous administ tion of doses up to 20 mg/kg, no maternal toxicity was p duced in the rabbit, and no embryotoxicity or teratogenic was observed. There are, however, no adequate and w controlled studies in pregnant women. Ciprofloxacin sho be used during pregnancy only if the potential benefit ju fies the potential risk to the fetus. (See **WARNINGS.**)

Nursing Mothers: Ciprofloxacin is excreted in human m Because of the potential for serious adverse reactions infants nursing from mothers taking ciprofloxacin, a de sion should be made whether to discontinue nursing or discontinue the drug, taking into account the importance the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patier and adolescents less than 18 years of age have not be established. Ciprofloxacin causes arthropathy in juven animals. (See **WARNINGS.**)

ADVERSE REACTIONS

The most frequently reported events, without regard to dr relationship, among patients treated with intraveno ciprofloxacin were nausea, diarrhea, central nervous syste disturbance, local I.V. site reactions, abnormalities of liv associated enzymes (hepatic enzymes), and eosinophili Headache, restlessness, and rash were also noted in great than 1% of patients treated with the most common doses ciprofloxacin.

Local I.V. site reactions have been reported with the intr venous administration of ciprofloxacin. These reactions a more frequent if the infusion time is 30 minutes or les These may appear as local skin reactions which resol rapidly upon completion of the infusion. Subsequent intr venous administration is not contraindicated unless th reactions recur or worsen.

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

CARDIOVASCULAR: cardiovascular collapse, cardiopu monary arrest, myocardial infarction, arrhythmia, tachyca dia, palpitation, cerebral thrombosis, syncope, cardiac mu mur, hypertension, hypotension, angina pectoris

CENTRAL NERVOUS SYSTEM: convulsive seizures, para noia, toxic psychosis, depression, dysphasia, phobia depersonalization, manic reaction, unresponsivenes ataxia, confusion, hallucinations, dizziness, lightheaded ness, paresthesia, anxiety, tremor, insomnia, nightmares weakness, drowsiness, irritability, malaise, lethargy

GASTROINTESTINAL: ileus, jaundice, gastrointestina bleeding, *C. difficile* associated diarrhea, pseudomembra nous colitis, pancreatitis, hepatic necrosis, intestinal per foration, dyspepsia, epigastric or abdominal pain, vomit ing, constipation, oral ulceration, oral candidiasis, mout dryness, anorexia, dysphagia, flatulence

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

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

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

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (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

Also reported were agranulocytosis, prolongation of prothrombin time, and possible exacerbation of myasthenia gravis.

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

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:

BODY AS A WHOLE: change in serum phenytoin

CARDIOVASCULAR: postural hypotension, vasculitis

CENTRAL NERVOUS SYSTEM: agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis

GASTROINTESTINAL: constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.)

HEMIC/LYMPHATIC: agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time

METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium

MUSCULOSKELETAL: myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture

RENAL/UROGENITAL: albuminaria, candiduria, renal calculi, vaginal candidiasis

SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis

SPECIAL SENSES: anosmia
(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 creatinine, 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 (γ 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

The recommended adult dosage for urinary tract infections of mild to moderate severity is 200 mg I.V. every 12 hours. For severe or complicated urinary tract infections, the recommended dosage is 400 mg I.V. every 12 hours.

The recommended adult dosage for lower respiratory tract infections, skin and skin structure infections, and bone and joint infections of mild to moderate severity is 400 mg I.V. every 12 hours.

For severe/complicated infections of the lower respiratory tract, skin and skin structure, and bone and joint, the recommended adult dosage is 400 mg I.V. every 8 hours.

The recommended adult dosage for mild, moderate, and severe nosocomial pneumonia is 400 mg I.V. every 8 hours.

Complicated Intra-Abdominal Infections: Sequential therapy [parenteral to oral - 400 mg CIPRO® I.V. q 12 h (plus I.V. metronidazole) ➔ 500 mg CIPRO® Tablets q 12 h (plus oral metronidazole)] can be instituted at the discretion of the physician. Metronidazole should be given according to product labeling to provide appropriate anaerobic coverage.

The recommended adult dosage for empirical therapy of febrile neutropenic patients is 400 mg I.V. every 8 hours in combination with piperacillin sodium 50 mg/kg I.V. q 4 hours, not to exceed 24 g/day (300 mg/kg/day), for 7-14 days.

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 of Severity	Unit Dose	Frequency	Daily Dose
Urinary tract	Mild/Moderate	200 mg	q12h	400 mg
	Severe/Complicated	400 mg	q12h	800 mg
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q 8h	1200 mg
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q 8h	1200 mg
Skin and Skin Structure	Mild/Moderate	400 mg	q 12h	800 mg
	Severe/Complicated	400 mg	q 8h	1200 mg
Bone and Joint	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q 8h	1200 mg
Intra-Abdominal*	Complicated	400 mg	q12h	800 mg
Empirical Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin	400 mg 50 mg/kg	q 8h q 4h	1200 mg Not to exceed 24 g/day

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

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

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

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

Ciprofloxacin hydrochloride (CIPRO® Tablets) for oral administration are available. Parenteral therapy may be changed to oral CIPRO® Tablets when the condition warrants, at the discretion of the physician. For complete dosage and administration information, see CIPRO® Tablets package insert.

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 × 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.

INTRAVENOUS ADMINISTRATION

CIPRO® I.V. should be administered by intravenous infusion over a period of 60 minutes. Slow infusion of a dilute solution into a large vein will minimize patient discomfort and reduce the risk of venous irritation.

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 1–2 mg/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 this method or the "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.

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 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

If CIPRO® I.V. is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

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 flexible containers as follows:

VIAL:	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.

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.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537 / S-025
19-847 / S-012
19-857 / S-013
19-858 / S-011

MEDICAL REVIEW(S)

D1✓

Medical Review of NDA Labeling Supplements

NDA 19-537/S-025/CIPRO Tablets
NDA 19-847/S-012/CIPRO I.V. (1% ciprofloxacin solution)
NDA 19-857/S-013/CIPRO I.V. (0.2% ciprofloxacin in 5% dextrose)
NDA 19-858/S-011/CIPRO I.V. (1% ciprofloxacin in 0.9% NaCl)

SEP 26 1997

DATE SUBMISSIONS SENT: September 24, 1996
DATE SUBMISSIONS STAMPED: September 30, 1996
APPLICANT: Bayer Corporation
DRUG NAME: Ciprofloxacin hydrochloride
CATEGORY: Fluoroquinolone
DATE REVIEW STARTED: August 6, 1997
DATE REVIEW COMPLETED: August 12, 1997

MATERIAL REVIEWED

- **September 23, 1993:** Advisory Committee Minutes and Package
- **September 23, 1993:** Medical Officer's Summary of Discussion and Recommendations of the Anti-Infective Advisory Committee
- **October 28, 1994:** DAIDP letter to Miles Inc. (regarding labeling change recommendations as per September 23, 1993 Advisory Committee)
- **March 24, 1995:** Submissions by Miles Inc. (19-537/S-025, 19-847/S-012, 19-857/S-013, 19-858/S-011) in response to October 28, 1994 letter indicating that Miles does not wish to make labeling revisions with regard to CNS toxicity
- **May 15, 1996:** Labeling Review of March 24, 1994 submissions
- **June 17, 1996:** DAIDP "not approvable" letter to Bayer in response to May 24, 1995 supplemental new drug applications 19-537/S-025, 19-847/S-012, 19-857/S-013, 19-858/S-011
- **January 26, 1996:** Report on CNS Events for the Fluoroquinolone Antibiotics, Reports Evaluation Branch, Division of Epidemiology, CDER, FDA
- **September 24, 1996:** Current 8 volume NDA submission (IV Formulations NDAs 19-847/S-012, 19-857/S-013, 19-858/S-011)
- **September 24, 1996:** Current 15 volume NDA submission (Tablet Formulation NDA 19537/S025)
- **August 7, 1997:** Final Approved IV Label for NDAs 19-847/S-012, 19-857/S-013, and 19-858/S-011
- **August, 1997:** Review of COSTART database for post-marketing spontaneous CNS adverse events reports for ciprofloxacin

PURPOSE

The sponsor, Bayer Corporation, amended their labeling supplements in response to the Division of Anti-Infective Drug Products' June 17, 1996, nonapprovable letter to NDAs 19-537/S-025, 19-847/S-012, 19-857/S-013, 19-858/S-011 (Note: this letter mistakenly referred to sponsor's March 24, 1995 submission as the May 24, 1995 submission).

Specifically, this nonapprovable letter stated that the Bayer's March 24, 1995, labeling supplements did not adequately address the issue of CNS toxicity and provided proposed labeling revisions. Hence, the purpose of these labeling submissions is to respond to the Agency letter and revise the labeling.

*MO Comment: The sponsor's proposed changes to the **WARNINGS** and **PRECAUTIONS** sections of NDA supplements 19-847/S-012, 19-857/S-013, 19-858/S-011 and 19-537/S-025 are very similar to those requested by the agency. The sponsor's proposed changes to the **ADVERSE REACTIONS** section of the label significantly differs from the FDA June 17, 1996 letter.*

REGULATORY BACKGROUND

A summary of the September 23, 1993, Advisory Committee's Recommendations follows: (see **Appendix 1**)

- The Committee endorsed by a majority vote the concept of disparate labeling for the currently marketed fluoroquinolones regarding CNS toxicity
- Class labeling for the currently marketed fluoroquinolones should remain class labeling, but the Agency and pharmaceutical sponsors have some options about addressing differences in side-effects within the class labeling. Proposals to highlight the increased seizure reporting rate for lomefloxacin, as well as the relative lack of predisposing factors, are listed below.

- In the **WARNINGS** paragraph for lomefloxacin, the increased seizure reporting rate for lomefloxacin as compared to other quinolones should be mentioned.
- Distinguish the seizures associated with lomefloxacin based on the relative absence of predisposing factors.

Regarding CNS toxicity, the Division's October 28, 1994, letter to NDAs 19-537, 19-847, 19-857, and 19-858 requested that Bayer propose appropriate wording, to be used in the **WARNINGS** and **PRECAUTIONS** section of the FPLs based on the recommendations of the September 23, 1993, Advisory Committee meeting.

Bayer submitted NDA supplements 19-537/S-025, 19-847/S-012, 19-857/S-013, and 19-858/S-011 on March 24, 1995 and this was reviewed by the Division of Anti-Infective Drug Products (DAIDP). DAIDP disagreed with the proposed wording and found the application not approvable. DAIDP suggested the following changes to the labels (as outlined in the June 17, 1996 letter to Bayer):

WARNINGS
Paragraph two should be revised as follows:

"Convulsions, increased intracranial pressure, and toxic psychoses have been reported in patients receiving quinolones, including ciprofloxacin.

PRECAUTIONS
General:
The following paragraph was suggested to be added so that it becomes the second paragraph of this subsection:

Information for patients:

REVIEW OF LABELING

In the current submissions the sponsor proposes changes to the **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections of these labels. The **WARNINGS** section and **PRECAUTIONS** section will be reviewed together and the review of **ADVERSE REACTIONS** will follow.

WARNINGS and PRECAUTIONS sections

The sponsor has proposed that some of the statements regarding CNS toxicity (proposed in the Division's nonapprovable letter to NDAs 19-537/S-025, 19-847/S-012, 19-857/S-013, and 19-858/S-011) which were included in the **WARNINGS** section should be placed in **General,** Subsection**, PRECAUTIONS**. The sponsor responded by stating:

In addition, the sponsor changed the phrase:

to read as follows:

"Ciprofloxacin may also cause central nervous system (CNS) events including:..."

*Medical Officer Comments: CFR 21 201.57 addresses the **WARNINGS** section of the label and states that:*

"the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur."

It also states that "...a causal relationship need not have been proved."

It further states: "The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the 'Adverse Reactions' section of the label."

In the current submission, the sponsor provided the rates of CNS adverse events for ciprofloxacin according to their FOI database and clinical trial database for IV and PO therapy. This information is shown in **Table 1**.

Table 1: Incidence Rates, CNS Adverse Events
Which Appeared in DAIDP's June 17, 1996, Proposed Warning Section*

AEs	PO, IV & IV/PO Therapy		PO, IV & IV/PO Therapy		PO Therapy		IV & IV/PO Therapy	
	Cipro FOI Database Events (80 million scripts)	FOI Events Per million scripts	Cipro Clinical Trial Database Events (n=15494)	Clinical Trial Events Per 1000 courses	Cipro Clinical Trial database Events (n=11,525 courses)	Clinical Trial Events Per 1000 courses	Cipro Clinical Trial Database Events (n=3,969 courses)	Clinical Trial Events Per 1000 courses
Convulsions (including grand mal convulsions)	207	**2.6**	54	**3.5**	18	**1.6**	36	**9.1**
Dizziness	122	**1.5**	237	**15.3**	198	**17.2**	39	**9.8**
Confusion	121	**1.5**	89	**5.7**	25	**2.2**	64	**16.1**
Tremors	56	**0.7**	39	**2.5**	29	**2.5**	10	**2.5**
Hallucinations	112	**1.4**	31	**2.0**	13	**1.1**	18	**4.5**
Depression	17	**0.2**	27	**1.7**	15	**1.3**	12	**3.0**
Nervousness	*45*	***0.6***	*78*	***5***	*63*	***5.5***	*15*	***3.8***
Agitation	*39*	***0.5***	*28*	***1.8***	*5*	***0.4***	*23*	***5.8***
Insomnia	*31*	***0.4***	*101*	***6.5***	*75*	***6.5***	*26*	***6.6***
Anxiety	*22*	***0.3***	*24*	***1.5***	*8*	***0.7***	*16*	***4.0***
Paranoia	*9*	***0.1***	*5*	***0.3***	*1*	***0.1***	*4*	***1.0***
CNS Stimulation	*2*	***0***	*5*	***0.3***	*5*	***0.4***	-	-

* Terms in italics are those that were proposed (in the June 17, 1996 DAIDP letter) to be included in the **WARNINGS** section but moved to the **PRECAUTIONS** section in the sponsor's proposed label. Those not in italics were terms proposed (in the June 17, 1996 DAIDP letter) to be included in the **WARNINGS** section and were retained in the **WARNINGS** section of the sponsor's proposed label.
Note: the term "nightmares" was not included in the sponsor's table, but was moved from the **WARNINGS** section to the **PRECAUTIONS** section. The term "lightheadedness" and "restlessness" were removed from the **WARNINGS** section but not added to the **PRECAUTIONS** section by the sponsor.

Table 2 reviews the spontaneous reports submitted to the FDA of CNS toxicity for ciprofloxacin (IV and PO). Note that the spontaneous reporting does not provide information on drug use. Hence, this type of data is most useful when comparing the incidence of spontaneous adverse events (COSTART terms) for a specific drug.

Table 2: Number of the Most Common Spontaneous Reports for CNS Toxicity with Concurrent Ciprofloxacin (IV or PO) Use*

CNS COSTART terms	Spontaneous Reports
Convulsions	208
Confusion	160
Dizziness	157
Convulsions (Grand Mal)	86
Tremors	69
Agitation	57
Nervousness	55
Somnolence	47
Anxiety	38

*MO Comment: In general, the relative frequency of spontaneous reports of adverse from the FDA spontaneous adverse event reporting system during the post marketing period suggests that those terms which have been retained in the **WARNINGS** section of the label by the sponsor also are the most common relative to other CNS spontaneous adverse events. Hence, it is the opinion of the Medical Officer that the proposed changes to the **WARNINGS** section of the label are acceptable.*

*MO Comment: The Medical Officer concurs with the opinion of the sponsor that this paragraph (in the **PRECAUTIONS** section) is redundant. In addition, the September 23, 1993 Advisory Committee did not recommend the need for similar wording regarding CNS toxicity in both the **PRECAUTIONS** and **WARNINGS** section of the label.*

The June 17, 1996 FDA letter also suggested additional wording in the **Information for Patients** section as described above (see **REGULATORY BACKGROUND** section of this review). The September 23 Advisory Committee meeting concluded that a statement

should be included in this section regarding the risk of seizures in patients who are at high risk.

Bayer stated that the incidence rates do not support the Division's proposed statement and pointed to the Bayer clinical and FOI databases which demonstrate an incidence rate of [redacted] rescriptions, respectively..

MO Comment: The review of nervous system toxicity and adverse events with fluoroquinolones presented at the September 23, 1993 Advisory Committee meeting by the Division of Epidemiology and Surveillance suggested that most quinolone use at that time was due to ciprofloxacin [redacted] s compared with norfloxacin [redacted] ofloxacin [redacted] and lomefloxacin [redacted] prescriptions). In addition to the rates of CNS toxicity presented by the sponsor, this FDA review also suggested that the incidence of seizures during the post-marketing period is relatively low as compared with other quinolones. Rates per million prescriptions were reported as follows: ciprofloxacin [redacted] orfloxacin [redacted] oxacin 5.3, and lomefloxaci [redacted]

The *September 24, 1996 Advisory Committee (See* ***REGULATORY BACKGROUND*** *section above) stated that patients with predisposing factors should be advised that they are at increase risk for seizures or other central nervous system adverse events. The medical officer concurs with the Advisory Committee's recommendation. Although the incidence of spontaneous reports is fairly low, the sponsor's data from clinical trials suggesting a convulsion rate of 3.5/1000 is not insignificant. It is the opinion of the Medical Officer that the wording as stated in the June 17, 1996 letter is appropriate for all quinolones, including ciprofloxacin.*

ADVERSE REACTIONS section

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

- *The **PRECAUTIONS** sections of the labels as proposed by the sponsor are acceptable. However, the wording in the **Information for Patients** subsection of these labels should be retained as previously recommended in the June 17, 1996 "not approvable" letter.*
- *The **ADVERSE REACTIONS** sections of the labels should not be changed as proposed by the sponsor.* [redacted] *should not be included.*

Robert J. Hopkins MD

Robert J. Hopkins M.D., M.P.H., & T.M.

Concurrence:
HFD-590/Acting MOTL/MCavaille-Coll 9/8/97
HFD-590/DepDivDir/RAlbrecht 9/22/97

cc:
DIV. Files HFD-590
NDA 19-537/s-025
NDA 19-847/s-012
NDA 19-857/s-013
NDA 19-858/s-011
HFD-590/MO/RHopkins 9/8/97
HFD-735/Pharm/SSinger
HFD-590/CSO/PFogarty
HFD-590/CSO/MDempsy
HFD-590/CSO/LHubbard
HFD-520/TLMO/Malbuerne
HFD-590/MO/PCoyne
HFD-590/Acting TLMO/MCavaille-Coll
HFD-590/DepDivDir/RAlbrecht
HFD-590/DivDir/MGoldberger

Addendum to Medical Review of NDA Labeling Supplements

NDA 19-537/S-025/CIPRO Tablets
NDA 19-847/S-012/CIPRO I.V. (1% ciprofloxacin solution)
NDA 19-857/S-013/CIPRO I.V. (0.2% ciprofloxacin in 5% dextrose)
NDA 19-858/S-011/CIPRO I.V. (1% ciprofloxacin in 0.9% NaCl)

SUBMISSION STAMP DATE:	September 30, 1996
APPLICANT:	Bayer Corporation
DRUG NAME:	Ciprofloxacin hydrochloride
ADDENDUM DATE:	September 23, 1997

This addendum regards the reviewer's previous recommendation to keep the following statement in the **Information for Patients** section of the label:

In further discussing this need for this statement in the package insert, it was decided that it should not be required since the incidence of seizures associated with ciprofloxacin are thought to be comparable to other quinolones which currently do not have this statement in the **Information for Patients** section of the label.

Medical Officer Recommendation
It is recommended that the above statement not be included in either the IV or PO/suspension labels.

Robert J. Hopkins MD

Robert J. Hopkins M.D., M.P.H., & T.M.
Concurrence:
HFD-590/Acting MOTL/MCavaille-Coll 9/25/97
HFD-590/DepDivDir/RAlbrecht
cc:
DIV. Files HFD-590
NDA 19-537/s-025, NDA 19-847/s-012, NDA 19-857/s-013, NDA 19-858/s-011
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HFD-590/CSO/MDempsy
HFD-590/CSO/LHubbard
HFD-520/TLMO/Malbuerne
HFD-590/MO/PCoyne
HFD-590/Acting TLMO/MCavaille-Coll
HFD-590/DepDivDir/RAlbrecht 9/25/97
HFD-590/DivDir/MGoldberger MJG 9/26/97