

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

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 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.

CIPRO

Page 4

cc: Original NDA 20-780

HFD-590/Div. files

HFD-590/Goldberger

HFD-590/Hopkins

HFD-590/Coyne

HFD-590/Cavaille-Coll

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

9/25/97

Rut 9/25/97

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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

LABELING

the 7-position, and a cyclopropyl ring at the 1-position. Ciprofloxacin I.V. solutions are available as sterile 1.0% aqueous concentrations, which are intended for dilution prior to administration, and as 0.2% ready-for-use infusion solutions in 5% Dextrose Injection. All formulations contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1.0% aqueous concentrations 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						
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} × 2					
^c AUC _{24h} =AUC _{0-8h} × 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/L 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 usually exceed 400 µg/mL 0-2 hours after dosing and are generally 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.

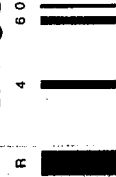
The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

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

PD500043

For Intravenous Infusion

CIPRO® I.V.
(ciprofloxacin)



CIPRO® I.V.
(ciprofloxacin)

For Intravenous Infusion

PD500043

10/97

CIPRO® I.V.
(ciprofloxacin)

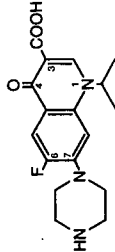
For Intravenous Infusion

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 C₁₇H₁₈N₄O₃ 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

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 dose adjustments may be required. (See **DOSE 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
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
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 aureus
Staphylococcus hominis

Aerobic gram-negative microorganisms
Acinetobacter lwoffii
Aeromonas hydrophila
Edwardsiella ictaluri
Enterobacter aerogenes
Klebsiella oxytoca
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*.

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 (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*:

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*:

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.

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*:

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 by 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.

rated 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. Standardized ciprofloxacin powder should provide the following MIC values:

Organism	MIC (µg/mL)
<i>E. faecalis</i>	ATCC 29212 0.25 - 2.0
<i>E. coli</i>	ATCC 25922 0.004 - 0.015
<i>H. influenzae</i> ^a	ATCC 49247 0.004 - 0.03
<i>N. gonorrhoeae</i> ^b	ATCC 49226 0.001 - 0.008
<i>P. aeruginosa</i>	ATCC 27853 0.25 - 1.0
<i>S. aureus</i>	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).²

^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 procedure² 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% CO₂.

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 disk techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized diffusion 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)
<i>E. coli</i>	ATCC 25922 30-40
<i>H. influenzae</i> ^a	ATCC 49247 34-42
<i>N. gonorrhoeae</i> ^b	ATCC 49226 48-58
<i>P. aeruginosa</i>	ATCC 27853 25-33
<i>S. aureus</i>	ATCC 29213 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*, *Neisseria pneumoniae* 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 18-84)	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 Success (%)	Tobramycin/Piperacillin Success (%)
Clinical Resolution of Initial Febrile Episode with No Modifications of Empirical Regimen ^a	63 (27.0%)	52 (21.9%)
Clinical Resolution of Initial Febrile Episode Including Cases with Modifications of Empirical Regimen	187 (80.3%)	185 (78.1%)
Overall Survival	224 (96.1%)	223 (94.1%)

^a 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 patient 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 (e.g., low seizure threshold). (See **PRECAUTIONS: General**.)

PRECAUTIONS: General 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 (e.g., low seizure threshold). (See **PRECAUTIONS: General**.)

PRECAUTIONS: General 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 (e.g., low seizure threshold). (See **PRECAUTIONS: General**.)

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PRECAUTIONS: General Ciprofloxacin should be

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 (1.1 and 1.1 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.)
HEMICLYMPHATIC: 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: albuminuria, 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 transaminase (TGT), 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 Ciprofloxacin I.V. q 12 h (plus oral metronidazole) → 500 mg Ciprofloxacin I.V. 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			
Indication	Type of Severity	Unit Dose	Frequency
Urinary Tract	Mild/Moderate	200 mg	q12h
	Severe/Complicated	400 mg	q12h
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h
	Severe/Complicated	400 mg	q8h
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h
Skin and Soft Structure	Mild/Moderate	400 mg	q12h
Bone and Joint	Severe/Complicated	400 mg	q8h
Intra-Abdominal*	Mild/Moderate	400 mg	q12h
	Severe/Complicated	400 mg	q12h
Empirical Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin	400 mg 50 mg/kg	q8h q4h

* used in conjunction with metronidazole. (See product labeling for prescribing information.)
† DUE TO THE DESIGNED PATTERNS (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)
≥ 30
5 - 29

Dosage
See usual dosage
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 × 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.

sion 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% (110 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
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:
20 mL
40 mL
STRENGTH
200 mg, 1%
400 mg, 1%
NDC NUMBER
0026-8552-20
0026-8554-54

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

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

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

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

References: 1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 7th 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 Drug 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 Board Meeting, March 31, 1993, Silver Spring, MD. Report attached. 4. FDA, CDER, Advisors and Consultants Staff. HED-21. 1901. Chapman Avenue, Room 200, Rockville, MD 20852, USA.



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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)

DIV

Medical Review of NDA Labeling Supplements

NDA 19-537/S-025/CIPRO Tablets

SEP 26 1997

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)

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 _____ prescriptions, 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 _____ s compared with norfloxacin _____ ofloxacin _____ and lomefloxacin _____ 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 _____ ofloxacin _____ oxacin 5.3, and lomefloxacin _____

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

- 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.
- _____ 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/RAIbrecht *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/MDempsey

HFD-590/CSO/LHubbard

HFD-520/TLMO/Malbuerne

HFD-590/MO/PCoyne

HFD-590/Acting TLMO/MCavaille-Coll

HFD-590/DepDivDir/RAIbrecht

HFD-590/DivDir/MGoldberger *MB*

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

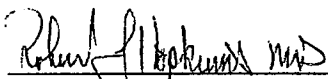
ADDENDUM DATE: September 23, 1997

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 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

HFD-590/MO/RHopkins

HFD-735/Pharm/SSinger

HFD-590/CSO/PFogarty

HFD-590/CSO/MDempsey

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 *9/26/97*