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
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

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

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

Dear Ms. Assumma:


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
APPLICATION NUMBER:

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

LABELING
The pharmacokinetics of ciprofloxacin are linear over the dose range of 200 to 400 mg administered intravenously. The serum elimination half-life is approximately 3 to 6 hours and the total clearance is around 50 L/hr. Comparison of the pharmacokinetic parameters following the 1st and 5th i.v. dose on a 12-hour interval failed to demonstrate any evidence of drug accumulation.

The absolute bioavailability of oral ciprofloxacin is within a range of 70-90% with no substantial loss by first pass metabolism. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes produces an AUC that is equivalent to that produced by a 400 mg oral dose given every 12 hours. 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 vs. time curve (AUC) equivalent to that produced by a 750 mg oral dose given every 12 hours. An intravenous dose of 400 mg ciprofloxacin given over 60 minutes every 12 hours is also similar to that observed with a 750 mg oral dose. An infusion of 200 mg ciprofloxacin given over 12 hours produces an AUC equivalent to that produced by a 230 mg oral dose given every 12 hours.

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 Dosing and Administration.) In preliminary studies in patients with stable chronic liver disease, no significant changes in ciprofloxacin pharmacokinetics have been observed. However, the kinetics of ciprofloxacin in patients with acute hepatic insufficiency have not been fully evaluated.

Following infusion of 400 mg i.v. ciprofloxacin every 8 hours in combination with 50 mg i.v. piperacillin sodium every 4 hours, the mean ciprofloxacin concentrations were 2.02 mg/L at 6 hours and 1.18 mg/L between 6-8 hours after the first dose.

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, bladder fluid, lymph, peripheral fluid, bile, and prostatic secretions. It has also been detected in the lungs, skin, fat, muscle, cartilage, bone, and bone marrow. Although the drug diffuses into cerebrospinal fluid, concentrations in cerebrospinal fluid are generally less than 10% of peak serum concentrations. Levels of the drug in the aqueous and vitreous humors 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. This antibacterial 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

<table>
<thead>
<tr>
<th>Organism</th>
<th>Minimum Inhibitory Concentration (MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>≤ 1 µg/mL</td>
</tr>
</tbody>
</table>

Aerobic gram-negative microorganisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Minimum Inhibitory Concentration (MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Haemophilus parainfluenza</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>≤ 1 µg/mL</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>≤ 1 µg/mL</td>
</tr>
</tbody>
</table>

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

Aerobic gram-positive microorganisms

<table>
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<tr>
<th>Organism</th>
<th>Minimum Inhibitory Concentration (MIC)</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Staphylococcus haemolyticus</td>
<td>≤ 1 µg/mL</td>
</tr>
</tbody>
</table>

Aerobic gram-negative microorganisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Minimum Inhibitory Concentration (MIC)</th>
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<tbody>
<tr>
<td>Escherichia coli</td>
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</tr>
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<td>Neisseria gonorrhoeae</td>
<td>≤ 1 µg/mL</td>
</tr>
</tbody>
</table>

This interpretive standard is applicable only to broth microdilution susceptibility tests with staphylococci using ciprofloxacin. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than Haemophilus influenzae, Haemophilus parainfluenzae, and Neisseria gonorrhoeae:

- Susceptible (S) ≤ 1 µg/mL
- Intermediate (I) 2-4 µg/mL
- Resistant (R) > 8 µg/mL

*These interpretive standards are applicable only to broth microdilution susceptibility tests with staphylococci using ciprofloxacin. The MIC values should be interpreted according to the following criteria:

For testing Haemophilus influenzae and Haemophilus parainfluenzae:

- Susceptible (S) ≤ 2 µg/mL
- Intermediate (I) 4-8 µg/mL
- Resistant (R) > 16 µg/mL
Organism District Zone Diameter (mm)

E. coli ATCC 25922 30-40
H. influenzae ATCC 49247 34-42
P. aeruginosa ATCC 27853 25-33
Pseudomonas aeruginosa ATCC 25922 20-25

These quality control limits are applicable to all H. influenzae ATCC 49247 testing using Haemophilus Test Paper Disk.

These quality control limits are applicable only to tests conducted using GC agar base and 1% defined growth supplement.

INDICATIONS AND USAGE
CIPROFLOXACIN (CIPROFLOXACIN) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed in the DOSAGES AND ADMINISTRATION sections below:

Urinary Tract Infections: Ciprofloxacin (CIPROFLOXACIN) is indicated for the treatment of lower urinary tract infections in adults and children. The duration of treatment is 4 days to 2 weeks, depending on the severity of the infection.

Respiratory Tract Infections: Ciprofloxacin (CIPROFLOXACIN) is indicated for the treatment of community-acquired pneumonia in adults and children. The duration of treatment is 5 days to 14 days, depending on the severity of the infection.

Gastrointestinal Tract Infections: Ciprofloxacin (CIPROFLOXACIN) is indicated for the treatment of acute bacterial gastroenteritis in adults and children. The duration of treatment is 4 days to 7 days, depending on the severity of the infection.

REFERENCES

Bayer Corporation
Princeton, New Jersey
400 Morgan Lane
West Haven, CT 06516 USA

Cation: Federal (USA) Law prohibits dispensing without prescription.

FOS200423 10/97 BAY 0302 2002-4-A-U.S. © 1997 Bayer Corporation 7661 Printed in U.S.A.
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 half-life.

Quinolones, including ciprofloxacin, have been associated with temporary elevations in serum creatinine in patients receiving ciprofloxacin concomitantly. Alterations in the serum levels of pheosphates (increased and decreased) have been reported in patients receiving concomitant quinolone therapy. The magnitude of these changes is not known.

The concomitant administration of ciprofloxacin with other anticoagulants, phenytoin, or theophylline may require adjustment in dosage and monitoring to avoid toxicity.

Ciprofloxacin is a fluoroquinolone with activity against a wide range of aerobic and anaerobic bacteria. It is active against many Gram-positive and Gram-negative bacteria, including some species resistant to other antibiotics. Ciprofloxacin is approved for the treatment of infections caused by these organisms.

Ciprofloxacin is not recommended for use in patients with renal insufficiency or who require dialysis. It is not recommended for use in patients with severe hepatic impairment or who require liver transplantation.

Ciprofloxacin is a fluoroquinolone that is active against a wide range of Gram-positive and Gram-negative bacteria. It is active against many species of bacteria, including some resistant to other antibiotics. Ciprofloxacin is approved for the treatment of infections caused by these organisms.

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Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued.

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 a number of patients who were involved in controlled clinical trials comparing ciprofloxacin (IV and I.V.P. sequences) with systemically active antipseudomonal beta-lactams, the adverse event profile of ciprofloxacin was comparable to that of comparator treatments.

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide clinical experience with quinolones, including ciprofloxacin, are:

- BODY AS A WHOLE: change in serum thyrotrin
- CARDIOVASCULAR: paroxysmal atrial fibrillation, ventricular arrhythmia
- CENTRAL NERVOUS SYSTEM: agitation, confusión, delirium, dysaesthesia, myoclonus, nightmares, psychic disturbance
- GASTROINTESTINAL: constipation, dyspepsia, flatulence, nausea, hepatitis, jaundice, pancreatitis, pseudoneutropenia
- GU: menstrual disorder, onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment
- HEMATOLYMPHATIC: agranulocytosis, hemolytic anemia, leukopenia, neutropenia, platelet dysfunction, prolongation of prothrombin time
- METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium, uric acid
- MUSCULO/ICETAL: myalgia, possible exacerbation of myasthenia gravis, tendinitis/tenosynovitis rupture
- RENAL/URETERAL: albuminuria, candiduria, renal colic, vaginal candidiasis
- SKIN/HYPERSENSITIVITY: amphoteric reactions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- SPECIAL SENSES: anemia

(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:

- Hematologic:
  - elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, and serum bilirubin
  - elevations of eosinophil and platelet counts, decreased platelet counts, hemoglobin, and/or hematocrit
- Renal:
  - elevations of serum creatinine, BUN, and uric acid
- Elevations of serum creatinine, phosphatase, alkaline phosphatase, and serum bilirubin (in patients receiving theophylline concurrently), blood glucose, and triglycerides.

Other changes occurring infrequently were: decreased leukocyte count, elevated erythrocyte count, immature WBCs, elevated serum calcium, elevation of serum glucose, decreased serum aspartate aminotransferase (AST) (or decreased BUN), decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum phosphorus, increased serum cholesterol. Other changes occurring rarely during administration of ciprofloxacin were: elevation of serum amylase, decreases of blood glucose, pancreatitis, leukocytosis, elevated sodium, eosinophilia, elevation of serum bilirubin, increased prothrombin time, hemolytic anemia, and bleeder diathesis.

DOSAGE

In the event of acute overdose, the patient should be carefully observed and given supportive treatment. Activated charcoal may be given. The fraction of the oral dose eliminated by the gastrointestinal tract is dependent on the amount of ciprofloxacin (>10%) is removed from the body after hemodialysis or peritoneal dialysis. In mice, rats, rabbits and dogs, significant toxicity including toxicokinetic changes was observed at intravenous doses of ciprofloxacin as low as 125 and 25 mg/kg.

The recommended adult dosage for urinary 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 or complicated infections the lower respiratory tract, skin, skin structures, and bone and joint, the recommended adult dosage is 400 mg I.V. every 8 hours.

The recommended adult dosage for uncomplicated gonococcal infection is 400 mg I.V. every 8 hours.

Complicated Intrabdominal Infections: Sequential therapy (parenteral for 48 to 72 hours, followed by oral dosing). Ciprofloxacin in 400 mg I.V. IMATID (12 mg/1 mg) can be administered at the discretion of the physician. Metronidazole should be given accounting to product labeling at a dose and frequency appropriate for the anaerobic component of the infection.

The recommended adult dosage for empirical therapy of febrile neutropenic patients is 400 mg I.V. every 8 hours in combination with an appropriate antibiotic (e.g., 30 mg/kg every 8 hours, not to exceed 24 g/day 400 mg/day). For empirically treated patients, select-virulence strains of 0.5 mg/mL, is stable for up to 14 days at refrigerated or room temperature storage.

Ciprofloxacin 0.9% Sodium Chloride Injection, USP

For either CIPROFLOXACIN I.V. is available also as a 0.25% Sodium Chloride Injection, USP (250 mL, 400 mL, 1000 mL) I.V. solutions in flexible containers of 100 mL or 200 mL. The solutions in flexible containers may be reinfused as described above.

CIPROFLOXACIN I.V. is for IV or IO administration concomitantly with another drug, each drug given separately in accordance with the recommended dosage and routes of administration for each drug.

HOW SUPPLIED

CIPROFLOXACIN I.V. (ciprofloxacin) is available as a clear, colorless, or yellowish yellow solution. CIPROFLOXACIN I.V. is available in 200 mg and 400 mg strengths. In both strengths, the concentrate is supplied in flexible containers as follows:

<table>
<thead>
<tr>
<th>UM</th>
<th>SIZE</th>
<th>STRENGTH</th>
<th>NOC NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>mL</td>
<td>200 mg</td>
<td>5939-65-8</td>
</tr>
<tr>
<td>10</td>
<td>mL</td>
<td>400 mg</td>
<td>5939-66-4</td>
</tr>
</tbody>
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FLEXIBLE CONTAINER: manufactured for Bayer Corporation by Abbott Laboratories, North Chicago, IL 60064

<table>
<thead>
<tr>
<th>UM</th>
<th>SIZE</th>
<th>NOC NUMBER</th>
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</thead>
<tbody>
<tr>
<td>500 mL, 3% Sodium Chloride</td>
<td>330 mg/mL</td>
<td>0236-8933-36</td>
</tr>
<tr>
<td>200 mL, 3% Sodium Chloride</td>
<td>165 mg/mL</td>
<td>0236-8934-36</td>
</tr>
</tbody>
</table>

FLEXIBLE CONTAINER: manufactured for Bayer Corporation by Baxter Healthcare Corporation, DePere, WI 54115

<table>
<thead>
<tr>
<th>UM</th>
<th>SIZE</th>
<th>NOC NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mL, 1% Sodium Chloride</td>
<td>100 mg/mL</td>
<td>0236-8577-36</td>
</tr>
<tr>
<td>500 mL, 1% Sodium Chloride</td>
<td>500 mg/mL</td>
<td>0236-8578-36</td>
</tr>
</tbody>
</table>

STORAGE

Store between 2 and 25°C (41 to 77°F). Protect from light, avoid excessive heat, keep free from freezing.

CIPROFLOXACIN I.V. (ciprofloxacin) is also available in a 120 mL Pharmacy Glass Container. Ciprofloxacin is also available as CIPROFLOXACIN (ciprofloxacin HCI) Tablets 100, 250, 500, and 750 mg.

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 50 mg/kg the effect on the joint was minimal. In a subsequent study in beagles, removal of weight-bearing from the joint for an extended period did not totally prevent them. Crystaluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin and related compounds. It is related to the reduced solubility of ciprofloxacin under alkaline conditions, which predisposes to bladder crystalluria. In man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria in rats without nephroplasty has been noted after intravenous doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephroplastic 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 (10 sec) produces pronounced hyperventilation 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 hyperventilation, 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.

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

References:

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

Caution: Federal (USA) Law prohibits dispensing without a prescription.

PPDS0043 10/97 BAY 6393 5202-44-I-USA 3/97 Bayer Corporation

Printed in U.S.A.
APPLICATION NUMBER:

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

MEDICAL REVIEW(S)
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)  

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  
- January 26, 1996: Report on CNS Events for the Fluoroquinolone Antibiotics, Reports Evaluation Branch, Division of Epidemiology, CDER, FDA  
- September 24, 1996: Current 15 volume NDA submission (Tablet Formulation NDA 19537/S025)  
- August, 1997: Review of COSTART database for post-marketing spontaneous CNS adverse events reports for ciprofloxacin

PURPOSE
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:

“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>
<thead>
<tr>
<th>AEs</th>
<th>PO, IV &amp; IV/PO Therapy</th>
<th>PO, IV &amp; IV/PO Therapy</th>
<th>PO Therapy</th>
<th>IV &amp; IV/PO Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cipro FOI Database Events (80 million scripts)</td>
<td>207</td>
<td>2.6</td>
<td>54</td>
<td>3.5</td>
</tr>
<tr>
<td>Convulsions (including grand mal convulsions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>122</td>
<td>1.5</td>
<td>237</td>
<td>15.3</td>
</tr>
<tr>
<td>Confusion</td>
<td>121</td>
<td>1.5</td>
<td>39</td>
<td>2.5</td>
</tr>
<tr>
<td>Tremors</td>
<td>56</td>
<td>0.7</td>
<td>39</td>
<td>2.5</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>112</td>
<td>1.4</td>
<td>31</td>
<td>2.0</td>
</tr>
<tr>
<td>Depression</td>
<td>17</td>
<td>0.2</td>
<td>27</td>
<td>1.7</td>
</tr>
<tr>
<td>Nervousness</td>
<td>45</td>
<td>0.6</td>
<td>78</td>
<td>5</td>
</tr>
<tr>
<td>Agitation</td>
<td>39</td>
<td>0.5</td>
<td>28</td>
<td>1.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>51</td>
<td>0.4</td>
<td>101</td>
<td>6.5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>22</td>
<td>0.3</td>
<td>24</td>
<td>1.5</td>
</tr>
<tr>
<td>Paranoia</td>
<td>9</td>
<td>0.1</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>CNS Stimulation</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* 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*

<table>
<thead>
<tr>
<th>CNS/COSTART Terms</th>
<th>Spontaneous Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsions</td>
<td>208</td>
</tr>
<tr>
<td>Confusion</td>
<td>160</td>
</tr>
<tr>
<td>Dizziness</td>
<td>157</td>
</tr>
<tr>
<td>Convulsions (Grand Mal)</td>
<td>86</td>
</tr>
<tr>
<td>Tremors</td>
<td>69</td>
</tr>
<tr>
<td>Agitation</td>
<td>57</td>
</tr>
<tr>
<td>Nervousness</td>
<td>55</td>
</tr>
<tr>
<td>Somnolence</td>
<td>47</td>
</tr>
<tr>
<td>Anxiety</td>
<td>38</td>
</tr>
</tbody>
</table>

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; 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 — lomefloxacin 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**
• 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.

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

Concurrence:
HFD-590/Acting MOTL/MCavaille-Coll
HFD-590/DepDivDir/RAalbrecht

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/RRHopkins
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/RAalbrecht
HFD-590/DirDir/MGoldberger
Addendum to Medical Review of NDA Labeling Supplements

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SUBMISSION STAMP DATE: September 30, 1996
APPLICANT: Bayer Corporation
DRUG NAME: Ciprofloxacin hydrochloride
ADDITIONAL 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
HFD-590/DepDivDir/RAlbrecht

cc:
DIV. Files HFD-590
HFD-590/MO/RHopkins
HFD-735/Pharm/SSinger
HFD-590/CSO/PFogarty
HFD-590/CSO/MDempsy
HFD-590/CSO/LHubbard
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