

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-537 / S-030, S-031, S-033

20-780 / S-001, S-002, S-003

Trade Name: Cipro

Generic Name: Ciprofloxacin

Sponsor: Bayer Corporation

Approval Date: September 17, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537 / S-030, S-031, S-033

20-780 / S-001, S-002, S-003

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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APPROVAL LETTER



DF

NDA 19-537/S-030/S-031/S-033
NDA 20-780/S-001/S-002/S-003/S-004

Food and Drug Administration
Rockville MD 20857

SEP 17 1998

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

Dear Ms. Assumma:

Please refer to your supplemental new drug applications (NDA) dated October 1, 1997, October 15, 1997, April 16, 1998, and August 12, 1998 received October 2, 1997, October 16, 1997, April 16, 1998, and August 13, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO[®] (ciprofloxacin hydrochloride) Tablets and CIPRO[®] (ciprofloxacin) Oral Suspension.

We acknowledge receipt of your submissions dated September 14, and September 16, 1998.

These supplemental new drug applications provide for the following changes to the label:

1. Addition of text and a chart in the **CLINICAL PHARMACOLOGY** section to read as follows:

“A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg I.V. dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.”

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| Steady-state Pharmacokinetic Parameter Following Multiple Oral and I.V. Doses | | | | |
|--|--|---------------------|---|---------------------|
| Parameters | 500 mg q12h, P.O. | 400 mg 12h, I.V. | 750 mg q12h, P.O. | 400 mg q8h, I.V. |
| AUC ($\mu\text{g}\cdot\text{hr/mL}$) | 13.7 ^a | 12.7 ^a | 31.6 ^b | 32.9 ^c |
| C _{max} ($\mu\text{g/mL}$) | 2.97 | 4.56 | 3.59 | 4.07 |
| ^a AUC _{0-12h} | ^b AUC _{24h} =AUC _{0-12h} x2 | | ^c AUC _{24h} =AUC _{0-8h} x3 | |

- Addition of the term "taste loss" under the category SPECIAL SENSES in the **Post-Marketing Adverse Events** subsection of the **ADVERSE REACTIONS** section of the labeling.
- Addition of information pertaining to the use of Cipro in Cystic Fibrosis patients to the **Pediatric Use** subsection of **PRECAUTIONS** section to conform with the Cipro Tablet and I.V. labeling. The second and third paragraphs of the **Pediatric Use** subsection of **PRECAUTIONS** should read as follows:

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

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the Ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of the sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other

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We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling dated September 16, 1998. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit 20 copies of the FPL as soon as it is 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 supplemental NDAs 19-537/S-030/S-031/S-033 and 20-780/S-001/S-002/S-003/S-004. Approval of this submission is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

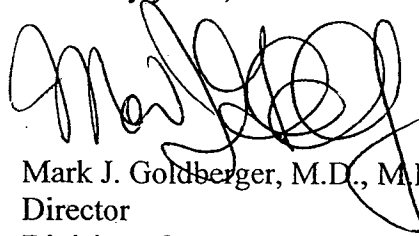
Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to those NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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

If you have any questions, please contact Mary Dempsey, Project Manager, at 301-827-2127.

Sincerely yours,



Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

NDA 19-537/S-030/S-031/S-033
NDA 20-780/S-001/S-002/S-003/S-004

cc:

Original NDA 19-537

NDA 20-780

HFD-590/Division files

HFD-

District Office

HFD-2/Medwatch (with labeling and review)

HFD-92 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling)

HFD-735 (with labeling -for all NDAs and supplements for adverse reaction changes.

HFD-021/JTreacy (with labeling)

HFD-590/DepDir/RAIbrecht

HFD-590/CPMS/EFrank

HFD-590/TLCHEM/NSchmuff

HFD-590/TLMICRO/SLard

HFD-590/TLPHARM/KHastings

HFD-590/TLBIOPHARM/FAjayi *ajs 9/17/98*

HFD-590/STAT/NSilliman

HFD-590/PM/MDempsey/Drafted 9/14/98

Concurrence Only:

HFD-590/TLMO/RHopkins *Pat 9-17-98*

HFD-590/CPMS/EFrank/*ecc/9-17-98*

HFD-590/TLBIOPHARM/FAjayi *ajs 9/17/98*

NDA 19-537/S-030/S-031/S-033

NDA 20-780/S-001/S-002/S-003/S-004

APPROVAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-537 / S-030, S-031, S-033

20-780 / S-001, S-002, S-003

LABELING

//

APPROVED

**CIPRO® (ciprofloxacin hydrochloride) TABLETS
CIPRO® (ciprofloxacin) 5% and 10% ORAL SUSPENSION**

SEP 17 1998

PXXXXXXX

9/98

DESCRIPTION

CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) Oral Suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is:

[STRUCTURE]

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:

[STRUCTURE]

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

CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg (ciprofloxacin equivalent) strengths. The inactive ingredients are starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a white to slightly yellowish suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (See instructions for USE/HANDLING). The components of the suspension have the following compositions:

Microcapsules - ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hydroxypropyl methylcellulose, magnesium stearate, and Polysorbate 20.

Diluent - medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor

recommended while 7 to 14 days is suggested for other mild/moderate, severe or complicated urinary tract infections.

The recommended adult dosage for chronic bacterial prostatitis is 500-mg every 12 hours.

The recommended adult dosage for oral sequential therapy of complicated intra-abdominal infections is 500-mg every 12 hours. (To provide appropriate anaerobic activity, metronidazole should be given according to product labeling.) (See CIPRO® I.V. package insert.)

Skin and skin structure infections and bone and joint infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

The recommended adult dosage for infectious diarrhea or typhoid fever is 500-mg every 12 hours. For the treatment of uncomplicated urethral and cervical gonococcal infections, a single 250-mg dose is recommended.

See Instructions To The Pharmacist for Use/Handling of CIPRO® Oral Suspension.

| DOSAGE GUIDELINES | | | | |
|------------------------------|----------------------|-----------|-------------|------------------|
| Infection | Type or Severity | Unit Dose | Frequency | Usual Durations† |
| Acute Sinusitis | Mild/Moderate | 500-mg | q 12 h | 10 days |
| Lower Respiratory Tract | Mild/Moderate | 500-mg | q 12 h | 7 to 14 days |
| | Severe/Complicated | 750-mg | q 12 h | 7 to 14 days |
| Urinary Tract | Acute Uncomplicated | 100-mg | q 12 h | 3 Days |
| | Mild/Moderate | 250-mg | q 12 h | 7 to 14 Days |
| | Severe/Complicated | 500-mg | q 12 h | 7 to 14 Days |
| Chronic Bacterial | Mild/Moderate | 500-mg | q 12 h | 28 Days |
| Prostatitis | | | | |
| Intra-Abdominal* | Complicated | 500-mg | q 12 h | 7 to 14 Days |
| Skin and Skin Structure | Mild/Moderate | 500-mg | q 12 h | 7 to 14 Days |
| | Severe/Complicated | 750-mg | q 12 h | 7 to 14 Days |
| Bone and Joint | Mild/Moderate | 500-mg | q 12 h | ≥ 4 to 6 weeks |
| | Severe/Complicated | 750-mg | q 12 h | ≥ 4 to 6 weeks |
| Infectious Diarrhea | Mild/Moderate/Severe | 500-mg | q 12 h | 5 to 7 Days |
| Typhoid Fever | Mild/Moderate | 500-mg | q 12 h | 10 Days |
| Urethral and Cervical | Uncomplicated | 250-mg | single dose | single dose |
| Gonococcal Infections | | | | |

* used in conjunction with metronidazole

† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared.

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

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

See Instructions for USE/HANDLING.

| <u>Dosage</u> | <u>Volume (mL) of Oral Suspension</u> | |
|---------------|---------------------------------------|------------|
| | <u>5%</u> | <u>10%</u> |
| 250-mg | 5 mL | 2.5 mL |
| 500-mg | 10 mL | 5 mL |
| 750-mg | 15 mL | 7.5 mL |

Complicated Intra-Abdominal Infections: Sequential therapy [parenteral to oral - 400-mg CIPRO[®] IV q 12 h (plus IV metronidazole) → 500-mg CIPRO[®] Tablets q 12 h (plus oral metronidazole)] can be instituted at the discretion of the physician.

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

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Chronic Bacterial Prostatitis should be treated for 28 days. Infectious diarrhea may be treated for 5-7 days. Typhoid fever should be treated for 10 days.

Concurrent Use With Antacids or Multivalent Cations: Concurrent administration of ciprofloxacin with sucralfate or divalent and trivalent cations such as iron or antacids containing magnesium, aluminum, or calcium may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. Therefore, concurrent administration of these agents with ciprofloxacin should be avoided. However, usual dietary intake of calcium has not been shown to alter the bioavailability of ciprofloxacin. Single dose bioavailability studies have shown that antacids may be administered either 2 hours after or 6 hours before ciprofloxacin dosing without a significant decrease in bioavailability. Histamine H₂-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Impaired Renal Function: Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through

the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment:

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

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

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

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

Women: 0.85 x the value calculated for men.

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

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

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

HOW SUPPLIED

CIPRO® (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing 100-mg or 250-mg ciprofloxacin. The 100-mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse side. The 250-mg tablet is coded with the word "CIPRO" on one side and "250" on the reverse side. CIPRO® is also available as capsule shaped, slightly yellowish film-coated tablets containing 500-mg or 750-mg ciprofloxacin. The 500-mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The 750-mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side. CIPRO® 250-mg, 500-mg, and 750-mg are available in bottles of 50, 100, and Unit Dose packages of 100. The 100-mg

strength is available only as CIPRO® Cystitis pack containing 6 tablets for use only in female patients with acute uncomplicated cystitis.

| | Strength | NDC Code | Tablet Identification |
|-----------------|----------|------------------|-----------------------|
| Bottles of 50: | 750-mg | NDC 0026-8514-50 | CIPRO 750 |
| Bottles of 100: | 250-mg | NDC 0026-8512-51 | CIPRO 250 |
| | 500-mg | NDC 0026-8513-51 | CIPRO 500 |
| Unit Dose | | | |
| Package of 100: | 250-mg | NDC 0026-8512-48 | CIPRO 250 |
| | 500-mg | NDC 0026-8513-48 | CIPRO 500 |
| | 750-mg | NDC 0026-8514-48 | CIPRO 750 |
| Cystitis | | | |
| Package of 6: | 100-mg | NDC 0026-8511-06 | CIPRO 100 |

Store below 30°C (86°F).

CIPRO® Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g ciprofloxacin in 100 mL) strengths. The drug product is composed of two components (microcapsules and diluent) which are mixed prior to dispensing. See Instructions To The Pharmacist For Use/Handling.

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

Microcapsules and diluent should be stored below 25°C (77°F) and protected from freezing.

Reconstituted product may be stored below 30°C (86°F). Protect from freezing. A teaspoon is provided for the patient.

ANIMAL PHARMACOLOGY

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

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral 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 at 3 and 10 mg/kg by rapid IV injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid IV 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.

CLINICAL STUDIES

Acute Sinusitis Studies

Ciprofloxacin tablets (500-mg BID) were evaluated for the treatment of acute sinusitis in two randomized, double-blind, controlled clinical trials conducted in the United States. Study 1 compared ciprofloxacin with cefuroxime axetil (250-mg BID) and enrolled 501 patients (400 of whom were valid for the primary efficacy analysis). Study 2 compared ciprofloxacin with clarithromycin (500-mg BID) and enrolled 560 patients (418 of whom were valid for the primary efficacy analysis). The primary test of cure endpoint was a follow-up visit performed approximately 30 days after the completion of treatment with study medication. Clinical response data from these studies are summarized below:

| Drug Regimen | Clinical Response Resolution at 30 Day Follow-up n(%) |
|---|--|
| STUDY 1 | |
| CIPRO 500-mg BID x 10 days | 152/197 (77) |
| Cefuroxime Axetil 250-mg BID x 10 days | 145/203 (71) |
| STUDY 2 | |
| CIPRO 500-mg BID x 10 days | 168/212 (79) |
| Clarithromycin 500-mg BID x 14 days | 169/206 (82) |

In ciprofloxacin-treated patients enrolled in controlled and uncontrolled acute sinusitis studies, all of which included antral puncture, bacteriological eradication/presumed eradication was documented at the 30 day follow-up visit in 44 of 50 (88%) *H. influenzae*, 17 of 21 (80.9%) *M. catarrhalis*, and 42 of 51 (82.3%) *S. pneumoniae*. Patients infected with *S. pneumoniae* strains whose baseline susceptibilities were intermediate or resistant to ciprofloxacin had a lower success rate than patients infected with susceptible strains.

Uncomplicated Cystitis Studies

Efficacy: Two U.S. double-blind, controlled clinical studies of acute uncomplicated cystitis in women compared ciprofloxacin 100-mg BID for 3 days to ciprofloxacin 250-mg BID for 7 days or control drug. In these two studies, using strict evaluability criteria and microbiologic and clinical response criteria at the 5-9 day post-therapy follow-up, the following clinical resolution and bacterial eradication rates were obtained:

| Drug Regimen | Clinical Response | Bacteriological Response By Organism (Eradication Rate) | |
|------------------------------|-------------------|---|------------------------------|
| | Resolution n(%) | <i>E. coli</i> n(%) | <i>S. saprophyticus</i> n(%) |
| STUDY 1 | | | |
| CIPRO 100-mg BID x 3 days | 82/94 (87) | 64/70 (91) | 8/8 (100) |
| CIPRO 250-mg BID x 7 days | 81/86 (94) | 67/69 (97) | 4/4 (100) |
| STUDY 2 | | | |
| CIPRO 100-mg BID x 3 days | 134/141 (95) | 117/123 (95) | 8/8 (100) |
| Control (3 days) | 128/133 (96) | 103/105 (98) | 10/10 (100) |

Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension:

Preparation of the suspension:

[IMAGE]

1. The small bottle contains the microcapsules; the large bottle contains the diluent.

[IMAGE]

2. Open both bottles. Child-proof cap: Press down according to instructions on the cap while turning to the left.

[IMAGE]

3. Pour the microcapsules completely into the large bottle of diluent. **Do not add water to the suspension.**

4. Remove the top layer of the diluent bottle label (to reveal the CIPRO ® Oral Suspension label).

[IMAGE]

5. Close the large bottle completely according to the directions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

Instructions To The Patient For Taking CIPRO ® Oral Suspension:

Shake vigorously each time before use for approximately 15 seconds.

Swallow the prescribed amount of suspension. Do not chew the microcapsules. Reclose the bottle completely after use according to the instructions on the cap. The suspension is stable for 14 days when stored in a refrigerator or at room temperature (below 86°F). After treatment has been completed, any remaining suspension should not be reused.

References: 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.
3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Product's Advisory Committee meeting, March 31, 1993, Silver Spring MD. Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA

Rx Only

CIPRO (R) (ciprofloxacin) 5% and 10% Oral Suspension made in Italy.

PXXXXXXX 9/98

Bay o 9867

5202-2-A-U.S.-6

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Printed in U.S.A.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-537 / S-030, S-031, S-033

20-780 / S-001, S-002, S-003

MEDICAL REVIEW(S)

DF

NDA 19-537/SLR-030

APR 8 1998

Medical Officer Review of Labeling Supplement

Submission date: 1 October 1997
Review completed: 31 March 1998

Applicant: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Drug: Trade: CIPRO
Generic: ciprofloxacin

Therapeutic category: fluoroquinolone antimicrobial

Dosage form: tablet

Route of administration: oral

Contents of submission: One volume

Purpose of supplement:

The applicant proposes to include text and a chart in the CLINICAL PHARMACOLOGY section describing the bioequivalence between the oral and intravenous dosing of ciprofloxacin. This information is already included in the CIPRO I.V. package insert. The applicant believes that it is "appropriate and important to also include this information in the labeling for the oral products."

Background:

This issue was discussed with the division during a conversation between Dr. Brad Leissa and Mr. Andrew Verderame of Bayer on 26 June 1997, at which time Dr. Leissa reportedly confirmed that such information is pertinent to the labeling of the oral dosage forms.

Material reviewed:

The applicant presents an annotated version of the CLINICAL PHARMACOLOGY section of the product labeling. Inserted after the second paragraph of the current label is the following language and table:

A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg I.V. dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

*Steady-state pharmacokinetic parameter
following multiple oral and i.v. doses*

| Parameters | 500 mg q12h, PO | 400 mg q12h, IV | 750 mg q12h, PO | 400 mg q8h, IV |
|--------------------------|--------------------|--------------------|--------------------|-------------------|
| AUC (μg•hr/mL) | 13.7 ^a | 12.7 ^a | 31.6 ^b | 32.9 ^b |
| C _{max} (μg/mL) | 2.97 | 4.56 | 3.59 | 4.07 |

footnotes:

a AUC_{0-12h}

b AUC 24 h = AUC_{0-12h} X 2

c AUC 24h = AUC_{0-8h} X 3

Medical officer comments:

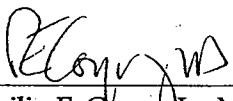
The proposed additions to the CLINICAL PHARMACOLOGY section are, indeed, identical to the text and table that was approved under supplements 19-847/S-005, 19-857/S-006 and 19-858/S-006 as per the approval letter dated 25 October 1995.

Medical officer conclusions:

Since these data relate the oral and IV dosage forms to one another, it is appropriate to include them in the oral dosage form label, as well as the intravenous label.

Medical officer recommendation:

The supplement should be approved, and a letter so stating should be provided to the applicant.


Philip E. Coyne, Jr., MD
Medical officer
HFD-590

cc: NDA 19-537/20-780
HFD-590/CSO/Dempsey
HFD-590/MO/Coyne
HFD-590/TL/Hopkins *RA it 4/8/98*
HFD-590/Chem/Schmuff
HFD-590/Pharm/Hastings
HFD-590/Micro/Dionne

info only:
HFD-590/DivDir/Goldberger
HFD-590/DepDivDir/Albrecht

DF

APR 8 1998

NDA 19-537/SLR-031

Medical Officer Review of Labeling Supplement

Submission date: 15 October 1997
Review completed: 31 March 1998

Applicant: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Drug: Trade: CIPRO
Generic: ciprofloxacin

Therapeutic category: fluoroquinolone antimicrobial

Dosage form: tablet

Route of administration: oral

Contents of submission: One volume

Purpose of supplement:

To add, under 21 CFR 314.70 "Special Supplement: Changes Being Effected", an event in the Post-Marketing Adverse Events subsection of the ADVERSE REACTIONS section of the combined package insert for CIPRO Tablets, and CIPRO 5% and 10% oral suspension. Under the category SPECIAL SENSES, the term 'taste loss' is proposed to be added.

Background:

The sponsor claims to have accumulated 25 reports of "taste loss" from US and international sources, which are included in the submission.

These reports are summarized in the following table:

Post-marketing reports of "Taste Loss" included in Supplement SLR-031

| Age/sex | Concomitant meds. | Reversible? | Comments |
|----------|--|-------------|---|
| 1. 56/F | Dyazide | Yes | -- |
| 2. 56/M | -- | No | Concomitant loss of smell |
| 3. 71/M | Aspirin | Yes | Concomitant loss of smell |
| 4. 34/F | Cefpodoxime proxetil | ? | Guillan-Barre syndrome suspected |
| 5. 57/F | -- | No | Concomitant loss of smell |
| 6. 67/M | -- | ? | -- |
| 7. 51/F | -- | No | Loss of salty taste specified |
| 8. ?/F | -- | No | Concomitant loss of smell |
| 9. 48/M | Metronidazole loperamide | ? | Concomitant loss of smell |
| 10. 69/M | Erythromycin salbutamol beclomethasone | No | Concomitant loss of smell |
| 11. 42/M | Atenolol enalapril lovastatin | No | Concomitant loss of smell |
| 12. 61/M | -- | No | Concomitant loss of smell |
| 13. 75/F | norfloxacin | ? | Concomitant hallucinations, hypotension, and SOB |
| 14. 61/M | Nifedipine | ? | Concomitant loss of smell |
| 15. 64/F | Bendrofluzide tibolone | No | Concomitant loss of smell |
| 16. 71/F | provastatin enalapril | No | Concomitant loss of smell |
| 17. 59/F | -- | No | Concomitant loss of smell |
| 18. 70/M | Entex LA | ? | -- |
| 19. 75/F | -- | ? | Concomitant loss of smell |
| 20. 61/M | Sinemet lisuride maleate biperiden HCl | No | Concomitant agitation, delusions |
| 21. 68/F | Propranalol erythromycin codiene | No | Concomitant loss of smell |
| 22. ?/F | -- | No | Concomitant loss of smell |
| 23. 55/F | Climagest primrose oil | No | Concomitant loss of smell |

Medical officer comments:

1. There were two reports of the original total of 25 that appeared to be duplicates of patient number 21 and were therefore deleted from this table. Thus, the more accurate total number of reports is 23.

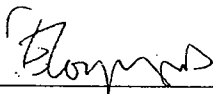
2. There does not appear to be any particular concomitant medication common in these episodes, thus making a drug-drug interaction unlikely.
3. The majority of the episodes reported concomitant loss of smell; this event is already included in the product labeling.
4. Many of the reported cases stated that the event was persisting, i.e., the loss of taste was not reversible.
5. Although not indicated in all of the reports, the majority of these events occurred following dosing with ciprofloxacin tablets. Few if any of these reports appeared to be in cases using the intravenous or suspension formulations.

Medical officer conclusions:

The proposed addition to the ADVERSE REACTIONS section is appropriate.

Medical officer recommendations:

The sponsor should be issued an 'approval' letter in response to this submission.



Philip E. Coyne, Jr., MD
Medical officer
HFD-590

cc: NDA 19-537
HFD-590/CSO/Dempsey
HFD-590/MO/Coyne
HFD-590/TL/Hopkins RV 4/2/97
HFD-590/Chem/Schmuff
HFD-590/Pharm/Hastings
HFD-590/Micro/Dionne

info only:
HFD-590/DivDir/Goldberger
HFD-590/DepDivDir/Albrecht