DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

Dear Ms. Christoforides:

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

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

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

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

1. **DESCRIPTION**

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

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

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

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

2. **CLINICAL PHARMACOLOGY**

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

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

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

- The following paragraph was added to read:

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

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

3. **INDICATIONS AND USAGE**

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

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

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

4. **CLINICAL STUDIES**

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

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

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

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

5. **PRECAUTIONS**

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

Information For Patients: Patients should be advised:

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

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

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

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

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

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

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

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

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

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

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

> There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]
>
> A controlled prospective observational study followed 200 women exposed to fluoroquinolones-(52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to one year of age in the ciprofloxacin exposed children.
>
> Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.
>
> No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).
>
> Reproduction studies have been performed in rats and mice using oral doses ~~of up to 100mg/kg (0.8 and 0.4 times the maximum daily human dose based upon body surface area, respectively) and I.V. doses of up to 30 mg/kg (0.24 and 0.12 times~~ up to 100

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

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

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

6. **ADVERSE REACTIONS**

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

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

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

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

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

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

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

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

8. **HOW SUPPLIED**

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

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

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

9. **STORAGE**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Renata Albrecht

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