DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-041
NDA 20-780/S-011

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 December 22, 2000, received December 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cipro® (ciprofloxacin hydrochloride) Tablets, 100 mg, 250 mg, 500 mg, 750 mg, and Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%.

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

Your submission of April 1, 2002 constituted a complete response to our January 31, 2002 action letter.

These supplements provide for the following changes to the Cipro® Tablet and Oral Suspension label. Deleted text is noted by ~~strikethrough~~ and added text is noted by double underline:

1. **DESCRIPTION**

- The description of tablet color and the word "corn" were added as follows:

> Ciprofloxacin tablets are white to slightly yellowish. CIPRO® ~~®~~ film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

- The following sentence referencing the Cipro Oral Suspension was added to the end of this section to read:

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

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.

•Under **Absorption**, the following sentence was added and is now the third sentence in the second paragraph:

> The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

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

3. The order of the indications in the **INDICATIONS AND USAGE** section was revised.

4. **PRECAUTIONS**

·The first bullet under **Information for Patients** was revised to read:

> ♦that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron or zinc should be avoided. ~~These products~~ Ciprofloxacin may be taken two hours ~~after or six hours before ciprofloxacin.~~ before or six hours after taking these products. Ciprofloxacin should not be taken ~~concurrently with milk or yogurt alone~~ dairy products (like milk or with yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced~~. Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption~~; however, ciprofloxacin may be taken with a meal that contains these products.

·The following paragraph was deleted in the **Drug Interactions** subsection:

> ~~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 is 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 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:

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

5. **ADVERSE REACTIONS**

・The first paragraph in this section was revised to read:

> During clinical investigation with the tablet, 2,799 patients received 2,868 courses of the drug. ~~Adverse events that were considered likely to be drug related occurred in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be possibly or probably related to drug therapy), and remotely related in 3.0%.~~ Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients treated~~, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%)~~.

・The following adverse events were added to this subsection:

> BODY AS A WHOLE: foot pain
>
> HEMIC/LYMPHATIC: lymphadenopathy

・The following sentence was deleted after the list of additional events:

> ~~"Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment."~~

・The following paragraph was deleted (was the fourth paragraph in this section):

> ~~In domestic clinical trials involving 214 patients receiving a single 250-mg oral dose, approximately 5% of patients reported adverse experiences without reference to drug relationship. The most common adverse experiences were vaginitis (2%), headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3%-1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness, and breast pain. Less than 20% of these patients had laboratory values obtained, and these results were generally consistent with the pattern noted for multi-dose therapy.~~

・In the **Post-Marketing Adverse Events** subsection, the following paragraph was added to replace the table of adverse events that previously existed:

> agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, flatulence, glucose elevation (blood), hemolytic anemia, hepatic necrosis, hypotension (postural), jaundice, methemoglobinemia, myalgia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, Stevens-Johnson syndrome, taste loss, tendinitis, tendon

rupture, toxic epidermal necrolysis, triglyceride elevation (serum), vaginal candidiasis, and vasculitis (See **PRECAUTIONS**.)

6. **OVERDOSAGE**

- The following sentence was moved and is now the last sentence in this section:

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.

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

8. **HOW SUPPLIED**

- The paragraph and table concerning Cipro Oral Suspension were revised as follows:

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 containing the active ingredient and diluent) which must be mixed by the pharmacist. ~~are mixed prior to dispensing.~~ See Instructions To The Pharmacist For Use/Handling.

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

9. The previous **CLINICAL STUDIES** section was deleted and replaced by the following**:**

Uncomplicated Cystitis

Two double-blind, controlled clinical studies of acute uncomplicated cystitis in women were performed in the U.S. At the 5-9 day post-therapy follow-up visit, the clinical resolution rates in the first study, which compared ciprofloxacin 100 mg BID for 3 days to ciprofloxacin 250 mg BID for 7 days, were 87% (82/94) and 94%, (81/86), respectively. For *E. coli*, the bacteriological eradication rates for the first study were 91% (64/70) in the ciprofloxacin 100 mg regimen and 97% (67/69) in the ciprofloxacin 250 mg regimen. The second study's bacteriological eradication rates were 95% (117/123) for the ciprofloxacin 100 mg regimen and 98% (103/105) for the control regimen. Pooled eradication rates for the ciprofloxacin 100 mg treatment arms were 100% (16/16) for *S. saprophyticus*.

10. **Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension**

- The following information was added to the beginning of this section:

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 must be combined prior to dispensing.

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.

Appropriate Dosing Volumes of the Oral Suspensions:

Dose	5%	10%
250-mg	5 mL	2.5 mL
500-mg	10 mL	5 mL
750-mg	15 mL	7.5 mL

- The following sentences were added to this section:

CIPRO Oral Suspension should not be administered through feeding tubes due to its physical characteristics.

Instruct the patient to shake CIPRO Oral Suspension vigorously each time before use for approximately 15 seconds and not to chew the microcapsules.

11. **Instructions To The Patient For Taking CIPRO® Oral Suspension** was deleted since a new patient package insert has been added to the end of this label.

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

13. A new section called "**PATIENT INFORMATION ABOUT CIPRO® (ciprofloxacin hydrochloride) TABLETS, CIPRO® (ciprofloxacin) ORAL SUSPENSION**" was added.

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

2. Please correct the spelling of the word "discarded" in the following sentence located in the "**Patient Information About Cipro**" section, **Cipro Oral Suspension** subsection of the package insert:

   "After treatment has been completed, any remaining suspension should be discarded."

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (package insert submitted April 1, 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 19-537/S-041, NDA 20-780/S-011." 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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