DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-847/SLR-028, SLR-029, SLR-031
NDA 19-857/SLR-033, SLR-034, SLR-036

Bayer Corporation Pharmaceutical Division
Attention: Andrew S. Verderame
Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

Please refer to your supplemental new drug applications, which were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 19-847 CIPRO® (ciprofloxacin) IV 1% Solution

Supplement	Date submitted	Date received
028	January 29, 2004	January 30, 2004
029	January 29, 2004	February 2, 2004
031	April 7, 2004	April 9, 2004

NDA 19-857 CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose

Supplement	Date Submitted	Date Received
033	January 29, 2004	January 30, 2004
034	January 29, 2004	January 30, 2004
036	April 7, 2004	April 9, 2004

We acknowledge receipt of your amendments to NDA 19-847/S-028, S-029 and NDA 19-857/S-033, S-034 dated April 7, 2004.

NDA 19-847/S-028 (IV 1%) and NDA 19-857/S-033 (IV 0.2%) were submitted as Changes Being Effected (CBE) and provide for antibacterial drug resistance labeling revisions as specified in the Division's September 11, 2003 letter. This CBE request letter was sent per the Final Rule entitled "**Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use "**(68FR 6062, February 6, 2003).

NDA 19-847/S-029 (IV 1%) and NDA 19-857/S-034 (IV 0.2%) were submitted as CBE and provide for additional safety information in the label. Revisions are included in the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the package insert.

NDA 19-847/S-031 (IV 1%) and NDA 19-857/S036 (IV 0.2%) were submitted as CBE and provide for revisions to the **WARNINGS** and **PRECAUTIONS** sections to add quinolone class labeling information to the package insert.

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

Changes for NDA 19-847/S-028 (IV 1%) and NDA 19-857/S-033 (IV 0.2%)

1. The following sentence was added at the beginning of the label under the Product Name:

   To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO IV and other antibacterial drugs, CIPRO IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

2. The following was added as the last paragraph in the **INDICATIONS AND USAGE** section:

   To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO IV and other antibacterial drugs, CIPRO IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

3. The following was added as the last paragraph in the **PRECAUTIONS**, **General** subsection:

   Prescribing CIPRO IV in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4. The following was added as the first bullet in the **PRECAUTIONS**, **Information for Patients** subsection:

   - that antibacterial drugs including CIPRO IV should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO IV is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken

exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CIPRO IV or other antibacterial drugs in the future.

Changes for NDA 19-847/S-029 (IV 1%) and NDA 19-857/S-034 (IV 0.2%)

1. Under the **CLINICAL PHARMACOLOGY**, **Excretion** subsection the following text was added at the end:

   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. The following text was added to the sixth paragraph of the **WARNINGS** section:

   After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile colitis*. Drugs that inhibit peristalsis should be avoided.

3. The following was added to the second bullet in the **PRECAUTIONS**, **Information for Patients** subsection:

   - 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.

4. The following text was revised in the **PRECAUTIONS, Drug Interactions** subsection**:**

   Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

   Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Non-steroidal anti-inflammatory ~~Metoclopramide accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.~~

~~Animal studies have shown that the~~ drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

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 $^{1}/2$ hour and 1.18 µg/mL between 6–8 hours after the end of infusion.

5. The following revisions were made in the **ADVERSE REACTIONS** section:

During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. 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 1.8% of intravenously treated patients.

The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

In clinical trials the following events were reported, ~~without regard to~~ regardless of drug relationship, ~~among~~ in greater than 1% of patients treated with intravenous ciprofloxacin: ~~were~~ nausea, diarrhea, central nervous system disturbance, local I.V. site reactions, liver function tests abnormal ~~abnormalities of liver associated enzymes (hepatic enzymes), and~~ eosinophilia, headache, restlessness, and rash. ~~were also noted in greater than 1% of patients treated with the most common doses of ciprofloxacin~~. Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no ~~treatment.~~ treatment. Local I.V. site reactions ~~have been reported with the intravenous administration of ciprofloxacin. These reactions~~ are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Additional medically important events, without regard to drug relationship or route of administration, that occurred in 1% or less of ciprofloxacin patients are listed below:

BODY AS A WHOLE: abdominal pain/discomfort, foot pain, pain, pain in extremities

CARDIOVASCULAR: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, atrial flutter, ventricular ectopy, (thrombo)-phlebitis, vasodilation, migraine

CENTRAL NERVOUS SYSTEM: convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy, abnormal gait, grand mal convulsion, anorexia

GASTROINTESTINAL: ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric ~~or abdominal~~ pain, ~~vomiting~~, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence, hepatitis, painful oral mucosa

HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time, lymphadenopathy, petechia

I.V. INFUSION SITE: thrombophlebitis, burning, pain, pruritus, paresthesia, erythema, swelling

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

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

RENAL/UROGENITAL: renal failure, interstitial nephritis, nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis, breast pain. Crystalluria, cylindruria, hematuria and albuminuria have also been reported.

RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea, laryngeal or pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough, bronchospasm

SKIN/HYPERSENSITIVITY: allergic reactions, anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae, hands or lower extremities, purpura, fever, chills, flushing, pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, thrombophlebitis, burning, paresthesia, erythema, swelling, photosensitivity (See **WARNINGS**.)

SPECIAL SENSES: decreased visual acuity, blurred vision, disturbed vision (flashing lights, change in color perception, overbrightness of lights, diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmus, chromatopsia, a bad taste

In several instances, nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin (I.V. and I.V. P.O. sequential) with intravenous beta-lactam control antibiotics, the CNS adverse event profile of ciprofloxacin was comparable to that of the control drugs.

Post-Marketing Adverse Events: The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Agitation, agranulocytosis, albuminuria, ~~anaphylactic reactions,~~ anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, monoliasis (oral, gastrointestinal, vaginal) myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendonitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

~~**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, tendonitis/tendon rupture, vaginal candidiasis (See **PRECAUTIONS**.)~~

Changes for NDA 19-847/S-031 (IV 1%) and NDA 19-857/S-036 (IV 0.2%)

1. The following text was added to the last two paragraphs of the **WARNINGS** section:

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

Tendon ~~Rupture:~~Effects: Ruptures of the shoulder, hand, ~~and~~ Achilles ~~and other tendon ruptures~~tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that ~~the~~ this risk may be increased in patients receiving concomitant corticosteroids, especially ~~in~~ the elderly. Ciprofloxacin should be discontinued if the patient

experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.

2. The following was added to the fifth bullet in the **PRECAUTIONS**, **Information for Patients** subsection:

- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.

We completed our review of these applications, as amended, and they are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert submitted April 7, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999*)* and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated **"FPL for approved supplements NDA 19-847/S-028, S-029, S-031 and NDA 19-857/S-033, S-034, S-036."** Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to each NDA and a copy to the following address:

MEDWATCH, HFD-410
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, R.N., M.B.A, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

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

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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