DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-048, S-050, S-051
NDA 20-780/S-012, S-014, S-015

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 #	Drug Product	Supplement Number	Letter Date	Receipt Date
19-537	Cipro® (ciprofloxacin hydrochloride) Tablets, 100 mg, 250 mg, 500 mg, 750mg	S-048	September 11, 2003	September 15, 2003
		S-050	January 26, 2004	January 27, 2004
		S-051	January 26, 2004	January 28, 2004
20-780	Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%	S-012	September 11, 2003	September 15, 2003
		S-014	January 26, 2004	January 27, 2004
		S-015	January 26, 2004	January 28, 2004

We acknowledge receipt of your submission dated November 7, 2003 for NDA 19-537/S-048, and your submissions dated February 25, 2004 for NDA 19-537/S-048, S-050, S-051, and NDA 20-780/S-012, S-014, S-015.

NDA 19-537/S-048 (tablets) and NDA 20-780/S-012 (oral solution**)** were submitted as Changes Being Effected (CBE) and provide for additional safety information in the label. Revisions are included in the **WARNINGS, PRECAUTIONS**, **ADVERSE REACTIONS**, and **OVERDOSAGE** sections of the package insert.

NDA 19-537/SLR-050 (tablets) and NDA 20-780/SLR-014 (oral solution) 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 19-537/SLR-051 (tablets) and NDA 20-780/ SLR-015 (oral solution) were submitted as Changes Being Effected (CBE) and provide for additional safety information in the label. Revisions are included in the **WARNINGS**, and **ADVERSE REACTIONS** sections of the package insert.

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:

NDA 19-537/S-048 (tablets) and NDA 20-780/S-012 (oral solution):

1. The following sentence was added to the **WARNINGS** section:

   Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Post-marketing surveillance reports indicate that the 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.

2. The **PRECAUTIONS**, **Drug Interactions** subsection was revised as follows**:**

   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~~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.

   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 combination of very high doses of quinolones and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

3. The **ADVERSE REACTIONS** section was revised as follows:

BODY AS A WHOLE: headache, abdominal pain/discomfort, foot pain, pain, pain in extremities, injection site reaction (ciprofloxacin intravenous)

CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypotension

CENTRAL NERVOUS SYSTEM: restlessness, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression paresthesia, abnormal gait, grand mal convulsion ~~(See above.) (See **PRECAUTIONS**.)~~

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding ~~(See above.) Cholestatic~~bleeding, cholestatic jaundice, hepatitis ~~jaundice has been reported.~~

HEMIC/LYMPHATIC: lymphadenopathy, petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism

SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema, nodosum, sweating
~~Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See **WARNINGS**.)~~

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

Post-Marketing Adverse Events: ~~Additional adverse events, regardless of relationship to drug,~~The following adverse events have been reported from worldwide marketing experience with quinolones, including ~~ciprofloxacin are:~~ 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, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

4. The **OVERDOSAGE** section was revised as follows:

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including monitoring of renal function and administration of magnesium or calcium containing antacids which can ~~treatment.~~ reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

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.

NDA 19-537/SLR-050 (tablets) and NDA 20-780/SLR-014 (oral solution):

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 Tablets and CIPRO Oral Suspension and other antibacterial drugs, CIPRO Tablets and CIPRO Oral Suspension 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 Tablets and CIPRO Oral Suspension and other antibacterial drugs, CIPRO Tablets and CIPRO Oral Suspension 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** section, **General:** subsection:

   Prescribing CIPRO Tablets and CIPRO Oral Suspension 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** section, **Information for Patients:** subsection:

   - that antibacterial drugs including CIPRO Tablets and CIPRO Oral Suspension should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO Tablets and CIPRO Oral Suspension 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 Tablets and CIPRO Oral Suspension or other antibacterial drugs in the future.

NDA 19-537/ SLR-051 (tablets) and NDA 20-780/ SLR-015 (oral solution):

1. The following sentence was added to the eighth 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.

2. The **ADVERSE REACTIONS** section was revised as follows:

SKIN/HYPERSENSITIVITY: allergic reaction, pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating

We completed our review of these applications 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 February 25, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 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-048, S-050, S-051 and NDA 20-780/S-012, S-014, S-015**." Approval of this submission 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 Christine Lincoln, 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 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

3/15/04 05:25:38 PM