DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-473/S-009

Bayer Pharmaceuticals Corporation
Attention: Ms. Janet Herrington
Deputy Director
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Herrington:

Please refer to your supplemental new drug application, which was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® XR (ciprofloxacin extended-release tablets) 500 mg and 1000 mg.

We acknowledge receipt of your submission dated January 14, 2005.

This "Changes Being Effected" supplemental new drug application provides for the following revisions to the package insert (additions are double underlined and deletions are ~~struck-out~~):

1. **CLINICAL PHARMACOLOGY**

- "Other highly buffered drugs" was added to the **Antacids** statement in the **Drug-drug Interactions** subsection as follows:

Antacids: When CIPRO XR given as a single 1000 mg dose was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible. (See **PRECAUTIONS, Information for Patients** and **Drug Interactions,** and **DOSAGE AND ADMINISTRATION**.)

2. **PRECAUTIONS**

- "Other highly buffered drugs" was added to **PRECAUTIONS, Information for Patients** and to the second paragraph in the **Drug Interactions** subsection as follows:

Information for Patients

- that CIPRO XR may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration with magnesium/aluminum antacids, or sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or with other products containing calcium, iron, or zinc should be avoided. CIPRO XR may be taken two hours before or six hours after taking these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.) CIPRO XR should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, CIPRO XR may be taken with a meal that contains these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.)

Drug Interactions

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for Patients,** and **DOSAGE AND ADMINISTRATION**.)

3. **ADVERSE REACTIONS**

- "Including life-threatening anaphylactic shock" and "Lyell's Syndrome" was added to the list of adverse events to read:

abnormal gait, achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions and including life-threatening anaphylactic shock), amylase increase, anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C. difficile* associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice, chromatopsia, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, fixed eruptions, flushing, gastrointestinal bleeding, gout (flare up), grand mal convulsion, gynecomastia, hallucinations, hearing loss, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic failure, hepatic necrosis, hepatitis, hiccup, hyperesthesia, hyperpigmentation, hypertension, hypertonia, hypesthesia, hypotension, ileus, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lipase increase, lymphadenopathy, manic reaction, marrow depression, migraine, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myocardial infarction, myoclonus,

nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, extremities, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, pancytopenia, paranoia, paresthesia, peripheral neuropathy, perspiration (increased), petechia, phlebitis, phobia, pleural effusion, polyuria, postural hypotension, prothrombin time prolongation, pseudomembranous colitis (the onset of symptoms may occur during or after antimicrobial treatment), pulmonary embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory distress, restlessness, serum sickness-like reaction, Stevens-Johnson syndrome, sweating, tachycardia, taste loss, tendonitis, tendon rupture, tinnitus, torsade de pointes, toxic epidermal necrolysis (Lyell's syndrome), toxic psychosis, twitching, unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing lights, change in color perception, overbrightness of lights).

4. OVERDOSAGE

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

In the event of acute excessive 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 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.

5. **DOSAGE AND ADMINISTRATION**

- "Other highly buffered drugs" was added to the **DOSAGE GUIDELINES** subsection to read:

CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible.

6. **HOW SUPPLIED**

- The "Bottles of 30" information was deleted and the NDC codes were revised to read:

	Strength	NDC Code	
~~Bottles of 30~~	~~500 mg~~	~~0026-8889-69~~	
Bottles of 50	500 mg	~~0026-8889-50~~	0085-1775-02
Bottles of 100	500 mg	~~0026-8889-51~~	0085-1775-01
Bottles of 50	1000 mg	~~0026-8897-50~~	0085-1778-03
Bottles of 100	1000 mg	~~0026-8897-51~~	0085-1778-01
Unit Dose Pack of 30	1000 mg	~~0026-8897-69~~	0085-1778-02

7. The company signature was revised to read:

Manufactured by:

Bayer HealthCare

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516
Made in Germany

Distributed by:

Schering-Plough

Schering Corporation
Kenilworth, NJ 07033

CIPRO is a registered trademark of Bayer Aktiengesellschaft and is used under license by Schering Corporation.

~~08852106,R.4~~ 08918573, R.0 Bay o 9867/q 3939 ~~4/04~~ 10/04 ~~12313~~ 12541

We completed our review of this application, as amended, and it is approved effective on the date of this letter.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter the 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 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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