DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-537/S-057
NDA 20-780/S-019

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 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, 250 mg, 500 mg, 750mg	S-057	November 15, 2004	November 19, 2004
20-780	Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%	S-019	November 15, 2004	November 19, 2004

We acknowledge receipt of your submissions dated January 12, 2005.

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the package insert (additions are <u>double underlined</u> and deletions are ~~struck out~~):

1. **PRECAUTIONS**

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

> •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, <u>other highly buffered drugs,</u> or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours before or six hours after taking these products. Ciprofloxacin 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, ciprofloxacin may be taken with a meal that contains these products.

Drug Interactions

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

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 decrease its absorption, resulting in serum and urine levels considerably lower than desired. (See **DOSAGE AND ADMINISTRATION** for concurrent administration of these agents with ciprofloxacin.)

2. ADVERSE REACTIONS

- "Including life-threatening anaphylactic shock" and "Lyell's Syndrome" was added to the list of **Post-Marketing Adverse Events** to read:

Agitation, agranulocytosis, albuminuria, anaphylactic reactions (including life-threatening anaphylactic shock), 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, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy, 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, torsade de pointes, toxic epidermal necrolysis (Lyell's Syndrome), triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

3. DOSAGE AND ADMINISTRATION-ADULTS

- "Other highly buffered drugs" was added to read:

Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder for oral solution, other highly buffered drugs, or other products containing calcium, iron or zinc.

- The reference to the 100 mg tablet was deleted from the **ADULT DOSAGE GUIDELINES** table to read:

Urinary Tract	Acute Uncomplicated	~~100 mg or~~ 250 mg	q 12 h	3 Days

4. **HOW SUPPLIED**

- This section was revised to read:

CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing ~~100 mg or~~ 250 mg ciprofloxacin. ~~The 100 mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse side.~~ The 250 mg tablet is coded with the word "CIPRO" on one side and "250" on the reverse side. CIPRO is also available as capsule shaped, slightly yellowish film-coated tablets containing 500 mg or 750 mg ciprofloxacin. The 500 mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The 750 mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side. CIPRO 250 mg, 500 mg, and 750 mg are available in bottles of 50, 100, and Unit Dose packages of 100. ~~The 100 mg strength is available only as CIPRO Cystitis pack containing 6 tablets for use only in female patients with acute uncomplicated cystitis.~~

	Strength	**NDC Code**	**Tablet Identification**
Bottles of 50:	750 mg	~~NDC 0026-8514-50~~ 0085-1756-01	CIPRO 750
Bottles of 100:	250 mg	NDC ~~0026-8512-51~~ 0085-1758-01	CIPRO 250
	500 mg	NDC ~~0026-8513-51~~ 0085-1754-01	CIPRO 500
Unit Dose Package of 100:	250 mg	NDC ~~0026-8512-48~~ 0085-1758-02	CIPRO 250
	500 mg	NDC ~~0026-8513-48~~ 0085-1754-02	CIPRO 500
	750 mg	NDC ~~0026-8514-48~~ 0085-1756-02	CIPRO 750
~~Cystitis Package of 6:~~	~~100 mg~~	~~NDC 0026-8511-06~~	~~CIPRO 100~~

Store below 30°C (86°F).

CIPRO Oral Suspension is supplied in 5% and 10% strengths. The drug product is composed of two components (microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist. See Instructions To The Pharmacist For Use/Handling.

Strengths	**Total volume after reconstitution**	**Ciprofloxacin Concentration**	**contents per bottle**	**Ciprofloxacin NDC Code**
5%	100 mL	250 mg/5 mL	5,000 mg	~~0026-8551-36~~ 0085-1777-01
10%	100 mL	500 mg/5 mL	10,000 mg	~~0026-8553-36~~ 0085-1773-01

Microcapsules and diluent should be stored below 25°C (77°F) and protected from freezing. Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing. A teaspoon is provided for the patient.

5. The next-to-the-last sentence under "**What is CIPRO?"** in the Patient Packet Insert (PPI) was revised to read:

   CIPRO Tablets are white to slightly yellow in color and are available in ~~100 mg,~~ 250 mg, 500 mg and 750 mg strengths.

6. The company signature was revised to read:

Manufactured by:

Bayer HealthCare

~~Bayer Pharmaceuticals Corporation~~
400 Morgan Lane
West Haven, CT 06516

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.

Rx Only

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08918468, R.0 10/04 Bay o 9867 5202-2-A-U.S.~~-16~~17 ~~1232~~012542
©2004 Bayer Pharmaceuticals Corporation Printed in U.S.A.
CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy.
CIPRO (ciprofloxacin HCl) Tablets Made in ~~U.S.A.~~Germany

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

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 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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