DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-065
NDA 19-847/S-039
NDA 19-857/S-046
NDA 20-780/S-024
NDA 21-473/S-022

Bayer Pharmaceuticals Corporation
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Dr. Herrington:

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

NDA Number	Drug Product	Supplement Number	Date of Supplement	Date of Receipt
19-537	CIPRO® (ciprofloxacin hydrochloride) Tablets, 250 mg, 500 mg, 750mg	065	May 24, 2007	May 25, 2007
19-847	CIPRO® IV (ciprofloxacin) 1% Solution in Vials, 200 mg, 400 mg	039	May 24, 2007	May 25, 2007
19-857	CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose, 200 mg, and 400 mg	046	May 24, 2007	May 25, 2007
20-780	CIPRO® (ciprofloxacin) Oral Suspension, 5% and 10%	024	May 24, 2007	May 25, 2007
21-473	CIPRO® XR (ciprofloxacin extended-release tablets) 500 mg and 1gm	022	May 24, 2007	May 25, 2007

These "Changes Being Effected" supplemental new drug applications provide for revisions to the package insert for Cipro® to ensure consistency in the communication of the risks of acute liver failure and acute severe liver injury, QTc prolongation/torsades de pointes, tendon rupture, toxic epidermal necrolysis (TEN), and *Clostridium difficile* associated disease (CDAD) with the use of antimicrobial products, including ciprofloxacin.

The following revisions (~~strikethrough~~ = deleted and <u>underlined</u> = added) to the text for the package insert for Cipro® and Cipro® XR were proposed in these supplemental applications:

Note: The revisions for both the Cipro® and Cipro® XR labels are identical. Where "Cipro/Cipro XR" is written below, it indicates that the label will read either "Cipro" or "Cipro XR", as appropriate.

1. The second paragraph in the **WARNINGS/Hypersensitivity Reactions** subsection was replaced with the underlined text below to provide greater clarity in the grouping of hypersensitivity findings. This subsection reads as follows:

~~Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.~~

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis;
- pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS/ Information for Patients** and **ADVERSE REACTIONS**).

2. The paragraphs regarding pseudomembranous colitis and *C. difficile* in the **WARNINGS** section were replaced with the following underlined text:

~~**Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in all patients who present with diarrhea subsequent to the administration of antibacterial agents.**~~
~~Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis". 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.~~

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRO/CIPRO XR, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

3. The **PRECAUTIONS/Information for Patients** subsection of the CIPRO® labeling was modified as follows:

   - to discontinue CIPRO treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those on corticosteroids.

4. The **PRECAUTIONS/Information for Patients** subsection of the CIPRO® XR labeling was modified as follows:

   - to discontinue CIPRO XR treatment; rest and refrain from exercise; and inform their physician ~~that~~ if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those on corticosteroids. ~~to discontinue treatment, to inform their physician, and to rest and refrain from exercise.~~

5. Under the **PRECAUTIONS/Information for Patients** subsection, the following text was added after the last bullet:

   - that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

6. Under the **PRECAUTIONS/Geriatric Use** subsection the following paragraphs were added following the current text:

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using CIPRO/CIPRO XR with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for torsades de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

Patients over 65 years of age are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO/CIPRO XR. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendon rupture usually involves the Achilles, hand, or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing CIPRO/CIPRO XR to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.

7. Under the **ADVERSE REACTIONS/Post-Marketing Adverse Events** subsection the following revision was made:

   hepatic failure (including fatal cases)

8. In the **"Patient Package Insert"** under the subsection **"What are the possible side effects of CIPRO/CIPRO XR?"** the following revisions were made:

   ~~CIPRO has been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPRO/CIPRO XR and call your health professional.~~

   Pain, swelling, and tears of Achilles, shoulder, or hand tendons have been reported in patients receiving fluoroquinolones, including CIPRO/CIPRO XR, The risk for tendon effects is higher if you are over 65 years old, and especially if you are taking corticosteroids. If you develop pain, swelling, or rupture of a tendon you should stop taking CIPRO/CIPRO XR, refrain from exercise and strenuous use of the affected area, and contact your health care provider.

9. In the **"Patient Package Insert"** under the subsection **"What are the possible side effects of CIPRO/CIPRO XR?"** the following paragraph was included:

   Diarrhea that usually ends after treatment is a common problem caused by antibiotics. A more serious form of diarrhea can occur during or up to 2 months after the use of antibiotics. This has been reported with all antibiotics including with CIPRO/CIPRO XR. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your physician as soon as possible.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions "**SPL for approved supplements NDA 19-537/S-065, NDA 19-847/S-039, NDA 19-857/S-046, NDA 20-780/S-024, and NDA 21-473/S-022.**"

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 this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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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