

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-473/S-005, S-006, S-007

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 21-473 CIPRO® (ciprofloxacin extended-release tablets)

Supplement	Date submitted	Date received
005	January 14, 2004	January 16, 2004
006	January 14, 2004	January 20, 2004
007	April 7, 2004	April 9, 2004

We acknowledge receipt of your amendments for NDA 21-473/S-005, S-006 dated April 7, 2004.

Supplement 005 was submitted as Changes Being Effected (CBE) and provides 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).

Supplement 006 was submitted as CBE and provides for additional safety information in the label. Revisions are included in the **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE** sections of the package insert.

Supplement 007 was submitted as CBE and provides for revisions to the **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections to add quinolone class labeling information to the package insert.

These supplements provide for the following changes to the Cipro® XR label. Deleted text is noted by ~~strike-through~~ and added text is noted by double underline:

Changes for NDA 21-473/S-005

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 XR and other antibacterial drugs, CIPRO XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

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 XR and other antibacterial drugs, CIPRO XR 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.

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

Prescribing CIPRO XR 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.

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

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

Changes for NDA 21-473/S-006

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

If a diagnosis of pseudomembranous colitis is 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 following revisions were made 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.

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.

Changes for NDA 21-473/S-007

1. The following revisions were made in the **PRECAUTIONS** section:

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesia, 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.
Achilles and other tendon ruptures-Tendon Effects: Ruptures of the shoulder, hand, Achilles 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 this risk may be increased in patients receiving with ciprofloxacin and other quinolones. concomitant corticosteroids, especially 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.

1. The following was added as a bullet in the **PRECAUTIONS** section, **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.
2. Torsade de pointes was added to the **ADVERSE REACTIONS** subsection.

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 21-473/S-005, S-006, S-007**". 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 Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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