DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-068
NDA 19-847/S-042
NDA 19-857/S-049
NDA 20-780/S-026
NDA 21-473/S-024

Bayer Pharmaceuticals Corporation
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, New Jersey 07045-1000

Dear Dr. Herrington:

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

Drug Product Name	**NDA Number**	**Supplement number**	**Date of supplement**	**Date of receipt**
CIPRO® (ciprofloxacin hydrochloride) Tablets	19-537	S-068	August 5, 2008	August 6, 2008
CIPRO® IV (ciprofloxacin) 1% Solution in Vials	19-847	S-042	August 5, 2008	August 6, 2008
CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19-857	S-049	August 5, 2008	August 6, 2008
CIPRO® (ciprofloxacin) Oral Suspension	20-780	S-026	August 5, 2008	August 6, 2008
CIPRO® XR (ciprofloxacin extended-release tablets)	21-473	S-024	August 5, 2008	August 6, 2008

We acknowledge receipt of your submissions dated September 5, September 25, and October 2, 2008.

Reference is also made to the FDA letter dated July 7, 2008 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for fluoroquinolone antimicrobial drugs. This information pertained to the risk of tendon-related adverse events with the use of fluoroquinolones.

Your supplemental new drug applications provide for revisions to the labeling for all CIPRO (ciprofloxacin) products, consistent with our July 7, 2008 letter and August 25, September 17, and October 2, 2008 correspondences.

These supplemental new drug applications provide for the following changes to product labeling (additions are noted by underline and deletions are noted by ~~strikethrough~~ replacing "CIPRO" with "CIPRO XR" where appropriate in the Cipro XR labeling):

1. A **Boxed Warning** with bolded font and enclosed in a black box was added to the beginning of the labeling as follows:

> **WARNING:**
> **Fluoroquinolones, including CIPRO®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).**

2. The **WARNINGS/Tendon Effects** subsection of the labeling was renamed "**Tendinopathy and Tendon Rupture**", moved to the first paragraph of the **WARNINGS** section, and updated as follows:

Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

~~**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 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.~~

3. The information on tendon adverse reactions in the **PRECAUTIONS/ Information for Patients** subsection of the labeling was moved to the first bullet of the subsection and updated as follows:

   - to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
   - ~~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 information on tendon adverse events in the **PRECAUTIONS/Geriatric Use** subsection of the labeling was moved to the first paragraph of the subsection and updated as follows:

   Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve~~s~~ the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue CIPRO and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

   ~~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. 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 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.~~

5. The Patient Package Insert for CIPRO Tablets, Oral Suspension, I.V., and CIPRO XR was replaced with a Medication Guide, and the complete Medication Guide is located at the end of the Package Insert.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the 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 to the enclosed labeling (text for the package insert, text for the patient package insert). 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-068, NDA 19-847/S-042, NDA 19-857/S-049, NDA 20-780/S-026, and NDA 21-473/S-024".**

In addition, within 21 days of the date of this letter, amend any pending applications for these NDAs with content of labeling in structured product labeling (SPL) format to include the changes approved in these applications.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter and that the revised labeling be reflected in the next printing of the labeling. While you may use labeling already printed as of the date of this letter until January 3, 2009, after that date we request that the revised labeling accompany any newly shipped product.

Failure to make these changes promptly could make your product misbranded under Sections 201(n) and 502(a) of FDCA.

Please note that you must comply with the Medication Guide Regulations as specified in 21 CFR 208. In particular, the carton and container labels must comply with 21 CFR208.24 (a)(2)(d). Please submit proposed labels for review within 30 days of receipt of this letter.

LETTERS TO HEALTH CARE PROFESSIONALS

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 these NDAs 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., Safety Regulatory 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 (Final Product Labeling, including Medication Guide)

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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