



NDA 19537/S-075  
NDA 19847/S-047  
NDA 19857/S-054  
NDA 20780/S-033  
NDA 21473/S-028

**SUPPLEMENT APPROVAL**

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

Dear Dr. Herrington:

Please refer to your Supplemental New Drug Applications (sNDA) 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 <sup>®</sup> (ciprofloxacin hydrochloride) Tablets	19537	S-075	December 15, 2010	December 15, 2010
CIPRO <sup>®</sup> IV (ciprofloxacin) 1% Solution in Vials	19847	S-047	December 15, 2010	December 15, 2010
CIPRO <sup>®</sup> IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19857	S-054	December 15, 2010	December 15, 2010
CIPRO <sup>®</sup> (ciprofloxacin) Oral Suspension	20780	S-033	December 15, 2010	December 15, 2010
CIPRO <sup>®</sup> XR (ciprofloxacin extended-release tablets)	21473	S-028	December 15, 2010	December 15, 2010

We acknowledge receipt of your amendments dated February 10, 2011.



We also refer to our letter dated November 15, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all fluoroquinolone products. This information pertains to the risk of fluoroquinolone-associated myasthenia gravis exacerbation, which is a potentially life-threatening event and may require ventilatory support.

These supplemental new drug applications provide for revisions to the labeling for CIPRO<sup>®</sup> (ciprofloxacin hydrochloride). The agreed upon changes to the language included in our November 15, 2010, letter are as follows (additions are noted by underline and deletion are noted by ~~striketrough~~, and replacing “CIPRO” with “CIPRO I.V.” and “CIPRO XR” where appropriate).

## I. BOXED WARNING

### **WARNING:**

**Fluoroquinolones, including CIPRO<sup>®</sup>, 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).**

**Fluoroquinolones, including CIPRO<sup>®</sup>, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid CIPRO<sup>®</sup> in patients with known history of myasthenia gravis (See Warnings).**

II. The following sub-section has been added after the **WARNINGS/Tendinopathy and Tendon Rupture** sub-section:

### **Exacerbation of myasthenia gravis**

**Fluoroquinolones, including CIPRO<sup>®</sup>, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid CIPRO<sup>®</sup> in patients with known history of myasthenia gravis. [See **PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**].**

III. **PRECAUTIONS/Information for Patients** has been revised as follows:

### **Information for Patients:**

Patients should be advised:

- 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<sup>®</sup> 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.
- that fluoroquinolones like CIPRO<sup>®</sup> may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.

**IV. ADVERSE REACTIONS/Post-Marketing Adverse Event Reports** section has been revised as follows:

**Post-Marketing Adverse Event Reports:** The following adverse events have been reported from worldwide marketing experience with fluoroquinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug. 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 (including fatal cases), hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, exacerbation of myasthenia gravis (~~possible exacerbation~~), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), photosensitivity/phototoxicity reaction, 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, tendinitis, tendon rupture, torsade de pointes, toxic epidermal necrolysis (Lyell's Syndrome), triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS.**)

**V. Medication guide:**

a. In the section "What is the most important information I should know about CIPRO<sup>®</sup>? The following has been added as the last bulleted paragraph:

- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like CIPRO may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section "**What are the possible side effects of CIPRO<sup>®</sup>?"** for more information about side effects

- b. In the section “**What should I tell my healthcare provider before taking CIPRO<sup>®</sup>?**” The following has been added:

**What should I tell my healthcare provider before taking CIPRO<sup>®</sup>?**

See "What is the most important information I should know about CIPRO<sup>®</sup>?"  
Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have a history of seizures
- have kidney problems. You may need a lower dose of CIPRO<sup>®</sup> if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- have trouble swallowing pills
- are pregnant or planning to become pregnant. It is not known if CIPRO<sup>®</sup> will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if CIPRO will harm your unborn child.
- are breast-feeding or planning to breast-feed. CIPRO passes into breast milk. You and your healthcare provider should decide whether you will take CIPRO or breast-feed.

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

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

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The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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## **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

## **REPORTING REQUIREMENTS**

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, call Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Ozlem Belen, MD, MPH  
Deputy Director for Safety  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

### **ENCLOSURE:**

Content of Labeling  
(CIPRO, CIPRO I.V., CIPRO XR)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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OZLEM A BELEN  
02/25/2011