DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-537/S-053, S-054
NDA 20-780/S-017, S-018

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 #	Drug Product	Supplement Number	Letter Date	Receipt Date
19-537	Cipro® (ciprofloxacin hydrochloride) Tablets, 100 mg, 250 mg, 500 mg, 750mg	S-053	April 7, 2004	April 9, 2004
		S-054	April 7, 2004	April 9, 2004
20-780	Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%	S-017	April 7, 2004	April 9, 2004
		S-018	April 7, 2004	April 9, 2004

NDA 19-537/S-053 (tablets) and NDA 20-780/S-017 (oral solution**)** were submitted as Changes Being Effected (CBE) and provide for additional safety information in the label. Revisions are included in the **PRECAUTIONS, Drug Interactions** subsection of the package insert.

NDA 19-537/SLR-054 (tablets) and NDA 20-780/SLR-018 (oral solution) were submitted as CBE and provide for the addition of quinolone class labeling in the **WARNINGS** section, **PRECAUTIONS**, **Information for Patients** subsection and **ADVERSE REACTIONS, Post-Marketing Adverse Events** subsection as was requested in the supplement request letter on November 26, 2003 and the facsimile from the Division dated March 10, 2004.

These supplements provide for the following changes to the Cipro® Tablet and Oral Suspension label. Deleted text is noted by ~~strikethrough~~ and added text is noted by <u>double underline</u>:

1. The following revisions were made under the **WARNINGS** section:

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, 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.

Tendon ~~Rupture:~~ Effects: Ruptures of the shoulder, hand, ~~and~~ Achilles ~~and other tendon ruptures~~ 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 ~~the~~ this risk may be increased in patients receiving concomitant corticosteroids, especially ~~in~~ 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.

2. The following bullet was added to the **PRECAUTIONS**, **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.

3. The following revisions were made under the **PRECAUTIONS**, **Drug Interactions** subsection:

   Non-steroidal anti-inflammatory ~~Animal studies have shown that the~~ drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

4. The following revisions were made under the **ADVERSE REACTIONS, Post-Marketing Adverse Events** subsection:

   Post-Marketing Adverse Events: The following adverse events have been reported from worldwide marketing experience with quinolones, 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, 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, ~~monoliasis~~ 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, torsades de pointes, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

We completed our review of these applications 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 19-537/S-053, S-054 and NDA 20-780/S-017, S-018."** 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 this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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