DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-537/S-062
NDA 20-780/S-023
NDA 19-847/S-037
NDA 19-857/S-042
NDA 21-473/S-016

Bayer Pharmaceuticals Corporation
Attention: Ms. Janet Herrington, Ph.D.
Deputy Director
400 Morgan Lane
West Haven, CT 06516-4175

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 #	Drug Product	Supplement Number	Letter Date	Receipt Date
19-537	CIPRO® (ciprofloxacin hydrochloride) Tablets, 250 mg, 500 mg, 750mg	S-062	December 29, 2005	December 30, 2005
20-780	CIPRO® (ciprofloxacin) Oral Suspension, 5% and 10%	S-023	December 29, 2005	December 30, 2005
19-847	CIPRO® (ciprofloxacin) IV 1% Solution Vials, 200 mg, 400 mg, and 1200 mg	S-037	December 29, 2005	December 30, 2005
19-857	CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose, 200 mg, and 400 mg	S-042	December 29, 2005	December 30, 2005
21-473	CIPRO® XR (ciprofloxacin extended-release tablets) 500 mg, 1gm	S-016	December 29, 2005	December 30, 2005

These supplements were submitted as Prior Approval (PA) supplements and provide for labeling changes to the **MICROBIOLOGY/Susceptibility Testing** subsection and to the **INDICATIONS and USAGE/Adult Patients** subsection of the package insert for NDA 19-537, NDA 20-780, NDA 19-847, and NDA 19-857. These labeling changes are being made in response to the supplement requested letter dated November 14, 2005.

The changes are outlined below for each of the three labels (Double underline=added text ~~Strikeout~~=deleted text).

NDA 19-537 and NDA 20-780 (Tablet and Oral Suspension)

1. **MICROBIOLOGY/Susceptibility Tests** subsection:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

~~For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:~~

For testing *Enterobacteriaceae*, *Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* [a]:

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ciprofloxacin disk should be interpreted according to the following criteria:
~~For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:~~

For testing *Enterobacteriaceae*, *Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* [a]:

2. **INDICATIONS AND USAGE/ Adult Patients** subsection:

Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-susceptible *Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*
Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.*
Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*
Lower Respiratory Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or penicillin-susceptible *Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*
Acute Sinusitis caused by *Haemophilus influenzae,* penicillin-susceptible *Streptococcus pneumoniae,* or *Moraxella catarrhalis.*
Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa,* ~~(~~methicillin-susceptible~~)~~, *Staphylococcus aureus,* methicillin-susceptible *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*
Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*
Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

NDA 19-847 and NDA 19-857 (IV)

1. **MICROBIOLOGY/Susceptibility Tests** subsection:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

~~For testing aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*[a]:~~
For testing *Enterobacteriaceae, Enterococcus faecalis,* methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae, Streptococcus pyogenes,* and *Pseudomonas aeruginosa*[a] :

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ciprofloxacin disk should be interpreted according to the following criteria:

~~For testing aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*[a]:~~

For testing *Enterobacteriaceae, Enterococcus faecalis,* methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae, Streptococcus pyogenes,* and *Pseudomonas aeruginosa* [a] :

2. **INDICATIONS AND USAGE/ Adult Patients** subsection:

Urinary Tract Infections caused by *Escherichia coli* (including cases with secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-susceptible *Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*
Lower Respiratory Infections caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or penicillin-susceptible *Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*
Nosocomial Pneumonia caused by *Haemophilus influenzae* or *Klebsiella pneumoniae.*
Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, ~~Staphylococcus aureus~~*(methicillin-susceptible)*~~,~~ Staphylococcus aureus,* methicillin-susceptible *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*
Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or

Pseudomonas aeruginosa.
Complicated Intra-Abdominal Infections (used in conjunction with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*
Acute Sinusitis caused by *Haemophilus influenzae,* penicillin-susceptible *Streptococcus pneumoniae,* or *Moraxella catarrhalis.*
Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*
Empirical Therapy for Febrile Neutropenic Patients in combination with piperacillin sodium. (See **CLINICAL STUDIES**.)

NDA 21-473 (extended-release)

1. **MICROBIOLOGY/Susceptibility Tests** subsection:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin. The MIC values should be interpreted according to the following criteria:
For testing *Enterobacteriaceae, Enterococcus* ~~species~~ *faecalis, Pseudomonas aeruginosa,* and *Staphylococcus* ~~species~~*saprophyticus:*

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ciprofloxacin disk should be interpreted according to the following criteria:
For testing *Enterobacteriaceae, Enterococcus* ~~species~~ *faecalis, Pseudomonas aeruginosa,* and *Staphylococcus* ~~species~~ *saprophyticus*:

We have completed the review of these supplemental new drug applications and they are approved effective upon the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the draft package insert submitted on December 29, 2005, for each label.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed.

Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions as "**FPL for approved supplements NDA 19-537/S-062, NDA 20-780/S-023, NDA 19-847/S-037, NDA 19-857/S-042, and NDA 21-473/S-016".** Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
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, please call Christine Lincoln, Project Manger, 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

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

6/19/2006 04:13:42 PM