DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-060
NDA 19-847/S-036
NDA 19-857/S-041
NDA 20-780/S-020
NDA 21-473/S-013

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

Dear Dr. Herrington:

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

Name of Drug Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Cipro® (ciprofloxacin hydrochloride) Tablets, 250 mg, 500 mg and 750 mg	19-537	S-060	May 6, 2005	May 9, 2005
Cipro® IV (ciprofloxacin) 1% Solution Vials, 200 mg, 400 mg and 1200 mg	19-847	S-036	May 12, 2005	May 13, 2005
Cipro® IV (ciprofloxacin) 0.2% Solution in 5% Dextrose, 200 mg and 400 mg	19-857	S-041	May 12, 2005	May 19, 2005
Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%	20-780	S-020	May 6, 2005	May 9, 2005
Cipro® XR (ciprofloxacin extended-release tablets), 500 mg and 1 gm	21-473	S-013	May 11, 2005	May 13, 2005

We acknowledge receipt of your submissions dated September 27, 2005 and November 8, 2005.

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the Cipro® package insert to include additional safety information regarding ciprofloxacin-tizanidine drug interactions:

Added text = <u>double underline</u> and Deleted text = ~~strikethrough~~

1. **Addition of ciprofloxacin's effect on CYP 450 ciprofloxacin-tizanidine interaction.**

CLINICAL PHARMACOLOGY
Metabolism
After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose. The binding of

ciprofloxacin to serum proteins is 20 to 40%. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug (see **CONTRAINDICATIONS; WARNINGS; PRECAUTIONS: Drug Interactions**).

Drug-drug Interactions: Concomitant administration with tizanidine is contraindicated. (See **CONTRAINDICATIONS).** The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **WARNINGS**; **PRECAUTIONS: Drug Interactions**.)

2. Addition of contraindication for concomitant use of ciprofloxacin with tizanidine.

CONTRAINDICATIONS
~~CIPRO (ciprofloxacin hydrochloride)~~ Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, ~~or~~ any member of the quinolone class of antimicrobial agents, or any of the product components.

Concomitant administration with tizanidine is contraindicated. (See **PRECAUTIONS: Drug Interactions**)

3. Addition of ciprofloxacin's effect on CYP 450 system.

WARNINGS
Cytochrome P450 (CYP450): Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g. theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug.

4. Addition of description on ciprofloxacin and tizanidine interaction.

PRECAUTIONS
Information for Patients:

Patients should be advised:

- that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that ciprofloxacin increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.

Drug Interactions: In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg bid for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

5. Revisions to the Patient Package Insert.

Patient Package Insert

Who should not take CIPRO?
You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones". You should also not take CIPRO if you are also taking a medication called tizanidine (Zanaflex®), as excessive side effects from tizanidine are likely to occur. CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO talk to your doctor before taking this medication. Due to possible side effects, CIPRO is not recommended for persons less than 18 years of age except for specific serious infections, such as complicated urinary tract infections.

What about other medications I am taking?
CIPRO can affect how other medicines work. Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. This is especially important if you are taking tizanidine (Zanaflex®) or theophylline. You should not take CIPRO if you are also taking tizanidine. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO.
Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO and may prevent it from working. Other medications such as sulcrafate and Videx® (didanosine) chewable/buffered tablets or pediatric powder may also stop CIPRO from working. You should take CIPRO either 2 hours before or 6 hours after taking these products.

We completed our review of these supplemental applications, as amended. These supplemental applications are approved, effective on 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 enclosed labeling (text for the package insert and text for the patient package insert submitted on November 8, 2005).

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 to be submitted in *pdf* format. To assist in our review of the FPL and future submission, 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, this submission should be designated "**FPL for approved supplements NDA 19-537/S-060, NDA 19-847/S-036, NDA 19-857/S-041, NDA 20-780/S-020, NDA 21-473/S-013**." Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
FDA
10903 New Hampshire Ave., Mail Stop 4447
Silver Spring, MD 20993-0002

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 Yon Yu, Pharm D., 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

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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