DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-085/S-019
NDA 21-277/S-011

Bayer Pharmaceuticals Corporation
Attention: Robin M. Christoforides
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications (sNDA) dated April 3, 2003, received April 7, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA #	Supplement #
AVELOX® (moxifloxacin hydrochloride) Tablets	21-085	S-019
AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V.	21-277	S-011

We acknowledge the receipt of your submissions dated April 30, 2003 and September 23, 2003.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

1. Under the **DESCRIPTION** section, ~~hydroxypropyl methylcellulose~~ was changed to hypromellose.

2. Under the **CLINICAL PHARMACOLOGY**, **Metabolism** subsection, the first sentence was revised to read:

   ~~Moxifloxacin~~ Approximately 52% of an oral or intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation.

3. Under the **CLINICAL PHARMACOLOGY, Special Populations, Geriatric** subsections**,** the first two sentences were revised as follows:

   Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and ~~16~~17 young (8 male;~~ 8~~9 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics. In 16 healthy ~~elderly~~ male ~~and female~~ volunteers ~~(66-81 years of age)~~ (8 young; 8 elderly) given a single 200 mg dose of oral moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was not statistically different between young and elderly males and elimination half-life was unchanged. No dosage adjustment is necessary based on age. In large phase III studies, the concentrations around the time of the end of the infusion in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients.

4. Under the **CLINICAL PHARMACOLOGY, Renal Insufficiency** subsection, the following revisions were made:

The pharmacokinetic parameters of moxifloxacin are not significantly altered ~~by~~in mild, moderate, ~~or severe renal impairment.~~severe, or end-stage renal disease. No dosage adjustment is necessary in patients with renal impairment, including those patients requiring hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).

In a single oral dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin were reduced by ~~22% and 21%~~21% and 28% in the patients with moderate ($CL_{CR} \geq 30$ and ≤ 60 mL/min) and severe ($CL_{CR} \leq 30$ mL/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients was increased by 13%. In the moderate and severe renally impaired patients, the mean AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and 1.4-fold (ranging up to 2.5-fold), respectively. ~~The sulfate and glucuronide conjugatesare not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal impairment has not been studied.~~

The ~~effect of~~ pharmacokinetics of single dose and multiple dose moxifloxacin were studied in patients with $CL_{CR} < 20$ mL/min on either hemodialysis or continuous ambulatory peritoneal dialysis ~~(CAPD) on the pharmacokinetics~~(8 HD, 8 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin ~~has not been studied.~~

in these HD and CAPD patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of moxifloxacin were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5 to 3, compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal disease including those undergoing HD and CAPD has not been studied.

Oral administration of 400 mg QD moxifloxacin for 7 days to patients on HD or CAPD produced mean systemic exposure (AUC_{ss}) to moxifloxacin similar to that generally seen in healthy volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Both HD and CAPD removed only small amounts of moxifloxacin from the body (approximately 9% by HD, and 3% by CAPD). HD and CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

5. Under the **CLINICAL PHARMACOLOGY, Drug-drug Interactions** subsection, "atenolol" was added as follows:

The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole, theophylline, warfarin, digoxin, atenolol, probenecid, morphine, oral contraceptives, ranitidine, glyburide, calcium, iron, and antacids has been evaluated. There was no clinically significant effect of moxifloxacin on itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives, or glyburide kinetics. Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine,

and calcium did not significantly affect the pharmacokinetics of moxifloxacin. These results and the data from *in vitro* studies suggest that moxifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 enzymes.

As with all other quinolones, iron and antacids significantly reduced bioavailability of moxifloxacin.

6. A new subsection was added between **Digoxin** and **Morphine** subsections in the **CLINICAL PHARMACOLOGY** section:

Atenolol: In a crossover study involving 24 healthy volunteers (12 male; 12 female), the mean atenolol AUC following a single oral dose of 50 mg atenolol with placebo was similar to that observed when atenolol was given concomitantly with a single 400 mg oral dose of moxifloxacin. The mean C_{max} of single dose atenolol decreased by about 10% following co-administration with a single dose of moxifloxacin.

7. Under the **WARNINGS** section, the first sentence of the second paragraph was revised as follows:

~~Because of limited clinical experience, moxifloxacin~~ Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 7,900 patients in controlled clinical studies, including 223 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 moxifloxacin tablet treated patients in a post-marketing observational study in which ECGs were not performed. (**See CLINICAL PHARMACOLOGY, Electrocardiogram**. For I.V. use see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS, Geriatric Use**.)

8. Under the **PRECAUTIONS**, **Drug Interactions** subsection**, "**atenolol" was added to the second paragraph:

No clinically significant drug-drug interactions between itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives or glyburide have been observed with moxifloxacin. Itraconazole, theophylline, digoxin, probenecid, morphine, ranitidine, and calcium have been shown not to significantly alter the pharmacokinetics of moxifloxacin. (See **CLINICAL PHARMACOLOGY**.)

9. Under the **ADVERSE REACTIONS**, HEMIC AND LYMPHATIC subsection, the following revisions were made:

   HEMIC AND LYMPHATIC: prothrombin decrease (prothrombin time prolonged/International Normalized Ratio (INR) increased), thrombocythemia, thrombocytopenia, eosinophilia, leukopenia

10. The last paragraph of the **ADVERSE REACTIONS** section was revised as follows:

    Additional clinically relevant rare events, judged by investigators to be at least possibly drug-related, that occurred in less than 0.1% of moxifloxacin treated patients were:

    abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation, convulsions, depersonalization, depression, diarrhea (*Clostridium difficile*), dysphagia, ECG abnormal, emotional lability, face edema, gastritis, hallucinations, hyperglycemia, hyperlipidemia, hypertonia, hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic), kidney function abnormal, parosmia, pelvic pain, prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR) decreased), sleep disorders, speech disorders, supraventricular tachycardia, taste loss, tendon disorder, thinking abnormal, thromboplastin decrease, tinnitus, tongue discoloration, urticaria, vasodilatation, ventricular tachycardia

11. The **ADVERSE REACTIONS, Post-Marketing Adverse Event Reports** subsection was revised as follows:

    Additional adverse events have been reported from worldwide post-marketing experience with moxifloxacin. 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. These events, some of them life-threatening, include anaphylactic reaction, anaphylactic shock, angioedema (including laryngeal edema), hepatitis (predominantly cholestatic), pseudomembranous colitis, psychotic reaction, Stevens-Johnson syndrome, syncope, ~~and~~ tendon rupture, and ventricular tachyarrhythmias (including in very rare cases cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions).

12. The **OVERDOSAGE** section was revised as follows:

    Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient should be carefully observed and given supportive treatment. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure. ~~It is not known whether moxifloxacin is removed by peritoneal or hemodialysis.~~

About 3% and 9% of the dose of moxifloxacin, as well as about 2% and 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and hemodialysis, respectively.

13. The **DOSAGE AND ADMINISTRATION**, **Impaired Renal Function** subsection was revised as follows:

No dosage adjustment is required in renally impaired patients~~. Moxifloxacin has not been studied in patients on~~, including those on either hemodialysis or continuous ambulatory peritoneal dialysis ~~(CAPD).~~

14. The second paragraph of the **DOSAGE AND ADMINISTRATION**, **Impaired Hepatic Function** subsection was revised as follows:

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with AVELOX I.V. may be switched to AVELOX Tablets when clinically indicated at the discretion of the physician.

AVELOX I.V. should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

15. The following paragraph was added to the end of the **ANIMAL PHARMACOLOGY** section:

In a local tolerability study performed in dogs, no signs of local intolerability were seen when moxifloxacin was administered intravenously. After inta-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

16. In the **Patient Information**, **What are the possible side effects of AVELOX?** subsection, "including Avelox" was added:

AVELOX is generally well tolerated. The most common side effects caused by AVELOX, which are usually mild, include dizziness, nausea, and diarrhea. If diarrhea persists call your healthcare provider. You should be careful about driving or operating machinery until you are sure AVELOX is not causing dizziness. If you notice any side effects not mentioned in this section or you have any concerns about the side effects you are experiencing, please inform your health care professional.

In some people, AVELOX, as with some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this has not caused any serious problems in more than 7,900 patients who have already taken the medication in clinical studies, in theory it could result in extremely rare cases of abnormal heartbeat which may be dangerous. Contact your health care professional if you develop heart palpitations (fast beating), or have fainting spells.

Convulsions have been reported in patients receiving quinolone antibiotics. Be sure to let your physician know if you have a history of convulsions. Quinolones, including AVELOX, have been

rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

Quinolones, including AVELOX, have been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking AVELOX and call your health care professional.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for package insert submitted September 23, 2003).

Please submit the copies of the final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* (January 1999). Please provide a Microsoft Word version of the FPL in the same submission with the PDF version. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-085/S-019 and NDA 21-277/s-011." 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 Professional" 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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Christine Lincoln, RN, MS, MBA, 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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