DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-006, S-007
NDA 21-277/S-002

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides
Assistant Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications dated August 31, 2000 and September 19, 2000, received September 1, 2000 and September 20, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avelox® (moxifloxacin HCL) Tablets, 400 mg.

Please also refer to your supplemental new drug application dated March 26, 2002, received March 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avelox® I.V. (moxifloxacin HCL in NaCl Injection) , 400 mg/250 ml 0.8% saline.

We acknowledge receipt of your submissions dated May 23, 2002 and May 29, 2002.

Your submission of May 23, 2002 constituted a complete response to our May 16, 2002 action letter.

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

1. DESCRIPTION

- The following sentence was deleted:

> "~~Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8-position, and an S,S – configured diazabicyclononyl ring moiety at the 7-position. ~~"

2. CLINICAL PHARMACOLOGY

- In the **Absorption** subsection, "male/female" was added to the first line in the IV dosing table and now reads:

"Healthy young male/female (n = 56)

- In the **Metabolism** subsection, the following sentence was added to the end of this subsection:

In vitro studies with cytochrome (CYP) P450 enzymes indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

- The first paragraph in the **Drug-drug Interactions** subsection was revised to read:

The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, oral contraceptive, ranitidine, glyburide, calcium, iron, and antacids has been evaluated. There was no clinically significant effect of moxifloxacin on itraconazole, theophylline, warfarin, digoxin, oral contraceptives, or glyburide kinetics. ~~Theophylline~~, Itraconazole, theophylline, warfarin, digoxin, probenecid, ~~and ranitidine~~ morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of moxifloxacin. These results and the data from *in vitro* studies suggests that moxifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 enzymes.

~~However,~~ ~~a~~As with all other quinolones, iron and antacids significantly reduced ~~the~~ bioavailability of ~~orally administered~~ moxifloxacin.

- The following new paragraphs were added in the **Drug-drug Interactions** subsection:

Itraconazole: In a study involving 11 healthy volunteers, there was no significant effect of itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the pharmacokinetics of moxifloxacin (a single 400 mg dose given on the 7^{th} day of itraconazole dosing). In addition, moxifloxacin was shown not to affect the pharmacokinetics of itraconazole.

Morphine: No significant effect of morphine sulfate (a single 10 mg intramuscular dose) on the mean AUC and C_{max} of moxifloxacin (400 mg single dose) was observed in a study of 20 healthy male and female volunteers.

Oral Contraceptives: A placebo-controlled study in 29 healthy female subjects showed that Moxifloxacin 400 mg daily for 7 days did not interfere with the hormonal suppression of oral contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered contraceptive agents.

Calcium: Twelve healthy volunteers were administered concomitant moxifloxacin (single 400 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement)

followed by an additional two dose of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no significant effect on the mean AUC of moxifloxacin. The mean Cmax was slightly reduced and the time to maximum plasma concentration was prolonged when moxifloxacin was given with calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours). These differences are not considered to be clinically significant.

• In the **Drug-drug Interactions** subsection, the first sentence of the **Electrocardiogram** paragraph was revised to read:

"Prolongation of the QT interval in the ECG has been observed in some patients receiving moxifloxacin."

3. WARNINGS

•The third and fourth paragraphs were revised to read:

Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be exercised when moxifloxacin ~~should be used with caution when~~ is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Because of limited clinical experience, 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 ~~drug~~ 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 ~~5000~~ 7900 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**.)

4. **PRECAUTIONS**

•In the **Information for Patients** subsection, the eighth bullet was revised to read:

•that moxifloxacin tablets should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium~~, calcium,~~ or aluminum), sucralfate, or Videx® (didanosine) chewable/buffered tablets or the pediatric

powder for oral solution. (See **CLINICAL PHARMACOLOGY**, **Drug Interactions** and **PRECAUTIONS**, **Drug Interactions**.)

•In the **Drug Interactions** subsection, the second sentence in the first paragraph was revised to read:

Oral administration of quinolones with antacids containing aluminum or magnesium ~~or calcium~~ with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired.

•In the **Drug Interactions** subsection, the second paragraph was revised to read:

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

5. ADVERSE REACTIONS

•The following "additionally relevant uncommon events" were revised to read:

BODY AS A WHOLE: headache, abdominal pain, injection site reaction, asthenia, moniliasis, pain, malaise, lab test abnormal (not specified), allergic reaction, leg pain~~,~~ back pain, ~~chills, infection,~~ chest ~~pain, hand~~ pain
RESPIRATORY: dyspnea~~, cough increased, pneumonia, pharyngitis, rhinitis, sinusitis~~
SKIN/APPENDAGES: rash (maculopapular, purpuric, pustular), pruritus, sweating~~, dry skin~~
UROGENITAL: vaginal moniliasis, vaginitis~~, cystitis~~

6. DOSAGE AND ADMINISTRATION

•The following paragraph was revised and the last sentence in this section was deleted. This now reads:

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to AVELOX I.V. or infused simultaneously through the same intravenous line. If the same intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the "piggyback" method of administration is used, the line should be flushed before and after infusion of AVELOX I.V. with an infusion solution compatible with AVELOX I.V as well as with other drug(s) administered via this common line.

~~If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of AVELOX I.V.~~

7. HOW SUPPLIED

- The Avelox Tablets packaging information was revised to read:

Package	**NDC Code**
Bottles of 30:	0026-8581-69
ABC Pack of 5:	0026-8581-41
Unit Dose ~~Package of~~ Pack of 50:	0026-8581-88

- The following statement was added to the Avelox Intravenous Solution packaging information:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. **DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION**.

8. PATIENT PACKAGE INSERT

- The "**What are the possible side effects of AVELOX**?" subsection was revised to read:

AVELOX is generally well tolerated. The most common side effects caused by AVELOX, which are usually mild, include nausea, ~~vomiting, stomach pain,~~ ~~diarrhea, dizziness~~ ~~and headache~~ diarrhea and dizziness. 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 ~~5000~~ 7900 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.

- The "**Which medicines should not be used with AVELOX?**" subsection was revised to read:

~~**Which medicines should not be used with AVELOX?**~~

What about other medicines I am taking?

Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. You should avoid taking AVELOX with certain medicines used to treat an abnormal heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

Some medicines also produce an effect on the electrocardiogram test, including cisapride, erythromycin, some antidepressants and some antipsychotic drugs. These may increase the risk of heart beat problems when taken with AVELOX. ~~For this reason it is important to let your health care provider know all of the medicines that you are using.~~

Many antacids and multivitamins may interfere with the absorption of AVELOX and may prevent it from working properly. You should take AVELOX either 4 hours before or 8 hours after taking these products.

We have completed the review of these supplemental 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. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted May 23, 2002).

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 21-085/S-006, S-007 and NDA 21-277/S-002." Approval of this submission 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 the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting 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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