DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-036
NDA 21-277/S-030

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

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	Date of supplement	Date of receipt
21-085	Avelox® (moxifloxacin hydrochloride) Tablets	S-036	April 20, 2007	April 23, 2007
21-277	Avelox® (moxifloxacin hydrochloride in NaCl injection) I.V.	S-030	April 20, 2007	April 23, 2007

These "Special Supplement - Changes Being Effected" supplemental new drug applications provide for revisions to the package insert for Avelox® to ensure consistency in the communication of the risks of acute liver failure and acute severe liver injury, QTc prolongation/torsades de pointes, tendon rupture, toxic epidermal necrolysis (TEN), and *Clostridium difficile* associated disease (CDAD) with the use of antimicrobial products, including moxifloxacin.

The following revisions (~~strikethrough~~ = deleted and <u>underlined</u> = added) to the text for the package insert for Avelox were proposed in these supplemental applications:

1. The second paragraph in the **WARNINGS** section (the first paragraph regarding QT prolongation) should not be in bolded font; it should written in regular font. A section heading of **"QT prolongation"** has been added above this paragraph.

2. The seventh paragraph in the **WARNINGS** section (the second paragraph regarding hypersensitivity) was replaced with the double underlined text below to provide greater clarity in the grouping of hypersensitivity findings. A subsection heading of **Hypersensitivity Reactions** was added before the sixth paragraph. This subsection reads as follows:

   <u>Hypersensitivity Reactions</u>
   Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including AVELOX. Some reactions were accompanied by

cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. AVELOX should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, may be administered as indicated.

~~Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.~~

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including AVELOX. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia;myalgia; serum sickness;
- allergic pneumonitis
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leucopenia; agranulocytosis; pancytopenia; and/or other hemotologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).

3. The eight and ninth paragraphs in the **WARNINGS** section (the paragraphs regarding pseudomembranous colitis and *C. difficile*) were replaced with the underlined text below:

~~**Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in all patients who present with diarrhea subsequent to the administration of antibacterial agents.**~~
~~Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis~~.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AVELOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

4. Under the **PRECAUTIONS/Information for Patients** subsection, the text was modified to read:

   - to discontinue AVELOX treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those on corticosteroids.

5. Under the **PRECAUTIONS/Information for Patients** subsection the following text was added after the last bullet:

   - that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

6. The **PRECAUTIONS/Geriatric Use** subsection was modified as follows:

   In controlled multiple-dose clinical trials, 23% of patients receiving oral moxifloxacin were greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The clinical trial data demonstrate that there is no difference in the safety and efficacy of oral moxifloxacin in patients aged 65 or older compared to younger adults.

   In trials of intravenous use ~~trials, in community acquired pneumonia, 45%~~ 42% of moxifloxacin patients were greater than or equal to 65 years of age, and ~~24%~~23% were greater than or equal to 75 years of age. The clinical trial data demonstrate that the safety of intravenous moxifloxacin in patients aged 65 or older was similar to that of comparator-treated patients. ~~In the pool of 491 elderly (> 65 years) patients, the following ECG abnormalities were reported in moxifloxacin vs. comparator patients: ST-T wave changes (2 events vs. 0 events), QT prolongation (2 vs. 0), ventricular tachycardia (1 vs. 0), atrial flutter (1 vs. 0), tachycardia (2 vs. 1), atrial fibrillation (1 vs. 0), supraventricular tachycardia (1 vs. 0), ventricular~~

~~extrasystoles (2 vs. 0), and arrhythmia (0 vs. 1). None of the abnormalities was associated with a fatal outcome and a majority of these patients completed a full course of therapy.~~

In general, elderly patients may be more susceptible to drug-associated effects of the QT interval. Therefore, AVELOX should be avoided in patients taking drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

Patients over 65 years of age are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone antibiotic such as AVELOX. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendon rupture usually involves the Achilles, hand or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing AVELOX to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.

7. Under the **ADVERSE REACTIONS/Post-Marketing Adverse Reactions** subsection, the following events were included:

   a. hepatic failure, including fatal cases
   b. toxic epidermal necrolysis

8. Under the **"Patient Package Insert,"** the following wording was included under "**What are possible side effects of AVELOX?"**

   ~~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 9200 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 healthcare provider right away if you have develop heart palpitations (fast beating) or have fainting spells.~~

   AVELOX may cause a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are increased in those with a family history of prolonged QT interval, low potassium (hypokalemia), and who are taking drugs to control heart rhythm, called class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. You should call your healthcare provider right away if you have any symptoms of prolongation of the QTc interval including prolonged heart palpitations (a change in the way your heart beats) or a loss of consciousness (fainting spells).

   ~~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.~~
   Pain, swelling, and tears of Achilles, shoulder, or hand tendons have been reported in patients receiving fluoroquinolones, including AVELOX, The risk for tendon effects is higher if you are over 65 years of age, and especially if you are taking corticosteroids. If you develop pain,

swelling, or tear of a tendon you should stop taking AVELOX, avoid exercise and strenuous use of the affected area, and contact your health care provider.

Diarrhea that usually ends after treatment is a common problem caused by antibiotics. A more serious form of diarrhea can occur during or up to 2 months after the use of antibiotics. This has been reported with all antibiotics including with AVELOX. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your physician as soon as possible.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions "**SPL for approved supplement NDA 21-085/S-036 and NDA 21-277/S-030**."

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Kristen Miller, 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

Enclosure

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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