



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-039

NDA 21-277/S-033

Bayer HealthCare Pharmaceuticals Inc.
Attention: Janet Herrington, Ph.D.
Deputy Director, Global Regulatory Affairs
PO Box 1000
Montville NJ 07045-1000

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 #	Supplement Number	Name of Drug Product	Date of Supplements	Date of Receipt
21-085	S-039	Avelox [®] (moxifloxacin hydrochloride) Tablets, 400 mg	June 27, 2008	June 30, 2008
21-277	S-033	Avelox [®] (moxifloxacin hydrochloride in NaCl injection) I.V., 160 mg/mL	July 23, 2008	July 24, 2008

We acknowledge receipt of your submissions dated November 3, 2008 and December 12, 2008.

These supplemental new drug applications propose revising the package insert for Avelox[®] (moxifloxacin) to add chemistry and safety information.

We have completed our review of these supplemental applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling. The final printed labeling (FPL) must be identical to the content of labeling for the package insert submitted on December 12, 2008.

The revisions to the package insert were as follows (additions are noted with underline and deletions noted with ~~strikethrough~~):

1. The last paragraph of the **DESCRIPTION** section was modified as follows:

AVELOX I.V. is available in ready-to-use 250 mL latex-free flexibags as a sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin) with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The color does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, USP, Water for Injection, USP, and

may include hydrochloric acid and/or sodium hydroxide for pH adjustment. AVELOX I.V. contains approximately 34.2 mEq (787 mg) of sodium in 250 mL.

2. In the **CLINICAL PHARMACOLOGY/Hepatic Insufficiency** subsection, the text was modified as follows:

No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency (Child-Pugh Classes A, B, or C). However, due to metabolic disturbances associated with hepatic insufficiency, which may lead to QT prolongation, moxifloxacin should be used with caution in these patients. (See WARNINGS and DOSAGE AND ADMINISTRATION). In 400 mg single oral dose studies in 6 patients with mild (Child Pugh Class A) and 10 patients with moderate (Child Pugh Class B), hepatic insufficiency, moxifloxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of controls. The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8-fold) in the mild and moderate groups, respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. (b) (4)

In a subset of (b) (4) patients participating in a clinical trial (b) (4) the plasma concentrations of moxifloxacin and metabolites determined approximately at the moxifloxacin T_{max} following the first intravenous or oral moxifloxacin dose in the Child-Pugh Class C patients (n=10) were similar to (b) (4) those in the Child-Pugh Class A/B patients (n=5), and also similar to (b) (4) those observed in healthy volunteer studies. (b) (4)

3. In the **WARNINGS/QT prolongation** subsection, the second paragraph was revised as follows:

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 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. 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 9,200 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.) In addition, moxifloxacin should be used with caution in patients with mild, moderate, or severe liver cirrhosis.

4. The **ADVERSE REACTIONS** section was modified as follows:

BODY AS A WHOLE: abdominal pain, headache, asthenia, dehydration (secondary to diarrhea or reduced fluid intake), injection site reaction (including phlebitis), malaise, moniliasis, pain, allergic reaction

CARDIOVASCULAR: cardiac arrhythmia (not otherwise specified), tachycardia, palpitation, vasodilation, QT interval prolonged

DIGESTIVE: vomiting, abnormal liver function test (increased transaminases, increased bilirubin), dyspepsia, dry mouth, flatulence, oral moniliasis, constipation, GGTP increased, anorexia, stomatitis, glossitis

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

METABOLIC AND NUTRITIONAL: lactic dehydrogenase increased, amylase increased

MUSCULOSKELETAL: arthralgia, myalgia

NERVOUS SYSTEM: insomnia, nervousness, vertigo, somnolence, anxiety, tremor

SKIN/APPENDAGES: rash (maculopapular, purpuric, pustular), pruritus, sweating, urticaria

SPECIAL SENSES: taste perversion

UROGENITAL: vaginal moniliasis, vaginitis

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 (visual disturbances temporally associated with CNS symptoms), agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation, back pain, chest pain, confusion, convulsions of various clinical manifestations (including grand mal convulsions), depersonalization, depression (potentially culminating in self-endangering behavior), dysphagia, dyspnea, ECG abnormal, emotional lability, face edema, gastritis, gastrointestinal disorder, hallucinations, hyperglycemia, hyperlipidemia, hypertension, hypertonia, hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic), kidney function abnormal, lab test abnormal (not specified), leg pain, paraesthesia, parosmia, pelvic pain, peripheral edema, photosensitivity/phototoxicity reactions, pseudomembranous colitis, prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR) decreased), sleep disorders, speech disorders, supraventricular tachycardia, syncope, taste loss, tendon disorder, thinking abnormal, thrombocytopenia, thromboplastin decrease, tinnitus, tongue discoloration, ventricular tachycardia

5. In the **ADVERSE EVENTS/Post-Marketing Adverse Event Reports** subsection, the text was modified as follows:

Additional adverse events have been reported from the worldwide postmarketing 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), hepatic failure, including fatal cases, hepatitis (predominantly cholestatic), photosensitivity/phototoxicity reaction (see **PRECAUTIONS**), psychotic reaction (very rarely culminating in self-endangering behavior), renal dysfunction or renal failure, Stevens-Johnson syndrome, tendon rupture, toxic epidermal necrolysis, and ventricular tachyarrhythmias (including in very rare cases cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions). Cases of altered coordination and abnormal gait have also been reported.

6. The **DOSAGE AND ADMINISTRATION/ Impaired Hepatic Function** subsection was revised as follows:

Impaired Hepatic Function

No dosage adjustment is ~~required in patients with~~ recommended for mild or, moderate hepatic insufficiency (Child-Pugh Classes A or B). ~~The pharmacokinetics of moxifloxacin in Patients with, or severe hepatic insufficiency (Child-Pugh Class Classes A, B, or C) have not been studied.~~ (See **CLINICAL PHARMACOLOGY, Hepatic Insufficiency.**)

CONTENT OF LABELING

As soon as possible, please submit the 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 to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, “**SPL for approved NDA 21-085/S-039 and NDA 21-277/S-033.**”

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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REPORTING REQUIREMENTS

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 Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 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: Package Insert

**This is a representation of an electronic record that was signed electronically and
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/s/

Rebecca Saville
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