



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-085/S-046
NDA 21-277/S-040

SUPPLEMENTS APPROVAL

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

Dear Dr. Herrington:

Please refer to your supplemental new drug applications dated and received on September 29, 2009 and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Drug Product
21-085	046	Avelox® (moxifloxacin) Tablets, 400 mg
21-277	040	Avelox® (moxifloxacin) I.V., 400 mg in 0.8% saline

We acknowledge receipt of your amendments dated January 14 and February 11, 2010.

These "Changes Being Effected" supplemental new drug applications propose revision of the labeling for the package insert to update information related to QT interval prolongation.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format submitted on February 11, 2010.

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

1. The **CLINICAL PHARMACOLOGY/Electrocardiogram** section of the labeling was revised as follows:

Electrocardiogram: Prolongation of the QT interval in the ECG has been observed in some patients receiving moxifloxacin. Following oral dosing with 400 mg of moxifloxacin the mean (\pm SD) change in QTc from the pre-dose value at the time of maximum drug

concentration was 6 msec (\pm 26) (n = 787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 10 msec (+22) on Day 1 (n = 667) and 7 msec (+ 24) on Day 3 (n = 667) 9 msec (+ 24) on Day 1 (n = 69) and on Day 3 (n = 290). (See **WARNINGS**.)

2. The **WARNINGS/QT prolongation** subsection of the labeling was revised as follows:

QT prolongation: Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

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 excess in cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 15,500^{9,200} patients in controlled clinical studies, including 759²²³ 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. (See **CLINICAL PHARMACOLOGY, Hepatic Insufficiency**.)

3. The first paragraph of the **ADVERSE REACTIONS** section of the package insert was updated to the following:

Clinical efficacy trials enrolled over 9,200^{15,500} moxifloxacin orally and intravenously treated patients, of whom over 8,600^{14,900} patients received the 400 mg dose. Most adverse events reported in moxifloxacin trials were described as mild to moderate in severity and required no treatment. Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 2.9% of orally treated patients and 6.3 % of sequentially (intravenous followed by oral) treated patients. The latter studies were conducted in community acquired pneumonia and complicated skin and skin structure infections and

complicated intra-abdominal infections with, in general, a sicker patient population compared to the tablet studies.

CONTENT OF LABELING

Within 14 days from the date of this letter, please amend all pending supplemental applications for these NDAs, including pending "Changes Being Effectuated" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in these supplemental applications.

LABELING

Submit final printed labeling as soon as they are available, but no more than 30 days after they are printed. The final printed labeling (FPL) must be identical to the enclosed labeling for the package insert submitted on February 11, 2010 and must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

The final printed labeling should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**Final Printed Labeling for approved NDA 21-085/S-046 and NDA 21-277/S-040.**" Approval of these submissions by FDA is not required before the labeling is used.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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If you have questions, call Rebecca D. McKinnon, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D.
Deputy Director of Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21085	SUPPL-46	BAYER HEALTHCARE PHARMACEUTICA LS INC	AVELOX (MOXIFLOXACIN HCL)
NDA-21277	SUPPL-40	BAYER HEALTHCARE PHARMACEUTICA LS INC	AVELOX (MOXIFLOXACIN HCL) IV 400MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OZLEM A BELEN
03/02/2010