



NDA 21085/S-047
NDA 21277/S-041

SUPPLEMENT APPROVAL

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

Dear Dr. Herrington:

Please refer to your Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Drug Product Name	NDA Number	Supplement number	Date of supplement	Date of receipt
AVELOX [®] (moxifloxacin hydrochloride) Tablets	21085	S-047	December 15, 2010	December 15, 2010
AVELOX [®] (moxifloxacin hydrochloride in NaCl injection) I.V	21277	S-041	December 15, 2010	December 15, 2010

We acknowledge receipt of your amendments dated January 25, 2011.



We also refer to our letter dated November 15, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all fluoroquinolone products. This information pertains to the risk of fluoroquinolone-associated myasthenia gravis exacerbation, which is a potentially life-threatening event and may require ventilatory support.

These supplemental new drug applications provide for revisions to the labeling for AVELOX[®] (moxifloxacin hydrochloride). The agreed upon changes to the language included in our November 15, 2010, letter are as follows (additions are noted by underline and deletion are noted by ~~striketrough~~).

I. BOXED WARNING

WARNING:

Fluoroquinolones, including AVELOX[®], are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see Warnings and Precautions (5.1)).

Fluoroquinolones, including AVELOX[®], may exacerbate muscle weakness in persons with myasthenia gravis. Avoid AVELOX[®] in patients with known history of myasthenia gravis. (see Warnings and Precautions (5.2)).

II. **5 WARNINGS AND PRECAUTIONS**, the following section has been added as follows:

5.2 Exacerbation of myasthenia gravis

Fluoroquinolones, including AVELOX, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid AVELOX in patients with known history of myasthenia gravis. [see Patient Counseling Information (17.3).

III. **Section 17.3 Serious and Potentially Serious Adverse Reactions** has been revised as follows:

To assure safe and effective use of AVELOX, patients should be informed of the following serious adverse reactions that have been associated with AVELOX and other fluoroquinolone use:

- **Tendon Disorders:** Patients should contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue AVELOX treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- **Exacerbation of Myasthenia Gravis:** fluoroquinolones like AVELOX may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.

IV. Medication guide:

- a. In the section **“What is the most important information I should know about AVELOX[®]?”** The following has been added as the last bulleted paragraph:

- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like AVELOX may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section "**What are the possible side effects of AVELOX[®]?**" for more information about side effects.

- b. In the section "**What should I tell my healthcare provider before taking AVELOX[®]?**" The following has been added:

What should I tell my healthcare provider before taking AVELOX[®]?

See "**What is the most important information I should know about AVELOX[®]?**"

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have low blood potassium (hypokalemia)
- have slow heart beat (bradycardia)
- have a history of seizures
- have kidney problems
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if AVELOX will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if AVELOX passes into breast milk. You and your healthcare provider should decide whether you will take AVELOX or breast-feed.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication

Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the

revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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, call Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:

Content of Labeling

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
02/25/2011