



NDA 21-085/S-014, S-015, S-017  
NDA 21-277/S-006, S-007, S-009

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

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications submitted December 17, 2002, received on December 18, 2002, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg (NDA 21-085/S-015) and AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V. (NDA 21-277/S-007).

We acknowledge receipt of your submissions dated:

January 31, 2003	February 12, 2003 (2)	February 26, 2003
February 3, 2003	February 19, 2003 (2)	
February 5, 2003 (2)	February 24, 2003	

These supplemental applications provide for the modification of the indication for Community Acquired Pneumonia to add “(including penicillin-resistant strains, MIC penicillin  $\geq 2\mu\text{g/mL}$ )” to *Streptococcus pneumoniae*. Specifically, the following changes to the package insert were made:

Double underline=added text

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- **MICROBIOLOGY** Section:

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

**Aerobic Gram-positive microorganisms**

*Staphylococcus aureus* (methicillin-susceptible strains only)

*Streptococcus pneumoniae* (including penicillin-resistant ~~susceptible~~ strains\* ~~only~~)

*Streptococcus pyogenes*

\*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of  $\geq 2\mu\text{g/mL}$

Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Aerobic Gram-positive microorganisms**

*Staphylococcus epidermidis* (methicillin-susceptible strains only)

*Streptococcus agalactiae*

*Streptococcus pneumoniae* (penicillin-resistant strains)

*Streptococcus viridans* group

- **INDICATIONS AND USAGE** Section:

**Community Acquired Pneumonia** caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 µg/mL), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*.

- **CLINICAL STUDIES** Section:

**Community Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)**

The clinical and bacteriological efficacy of AVELOX in the treatment of Community Acquired Pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC ≥ 2 µg /mL) was evaluated in 9 clinical studies: 4 comparative, double-blind tablet studies; 2 non-comparative, open-label tablet studies; 1 comparative, double-blind sequential intravenous to oral study; and 2 comparative, open-label, sequential intravenous to oral studies. All studies required strict assessment criteria with investigator assessment of treatment outcome as success or failure only. The primary efficacy parameter in these studies was clinical cure at the test-of cure visit, which ranged from Day 6 to 44 post-treatment. Of the 21 AVELOX-treated broth microdilution-confirmed valid for efficacy PRSP patients, 7 had PRSP bacteremia, 12 had severe pneumonia (by the Original American Thoracic Society criteria). The clinical success rates of *S. pneumoniae* and PRSP valid for efficacy patients are summarized in the following table.

<u>Pathogen</u>	<u>AVELOX</u>		<u>Comparators</u>	
	n/N	%	n/N	%
<u>All <i>S. pneumoniae</i></u>	<u>230/244</u>	<u>94</u>	<u>138/162</u>	<u>85</u>
<u><i>S. pneumoniae</i> bacteremia</u>	<u>53/58</u>	<u>91</u>	<u>35/41</u>	<u>85</u>
<u><i>S. pneumoniae</i> with Penicillin MIC ≥ 2 µg /mL</u>	<u>21/21*</u>	<u>100</u>	<u>5/5</u>	<u>100</u>

<u>S. pneumoniae bacteremia with Penicillin MIC ≥ 2 µg/mL</u>	<u>7/7</u>	<u>100</u>	<u>2/2</u>	<u>100</u>
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\*All of these patients were bacteriologic successes at the test-of-cure visit, and 7 of the 21 patients had MIC = 4 µg/mL

- **REFERENCES:** 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fifth Sixth Edition. Approved Standard NCCLS Document M7-A65, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 20030.
- 2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-~~Seventh~~ Eighth Edition. Approved Standard NCCLS Document M2-A87, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 20030.

- **Patient Information About: AVELOX® Section:**

AVELOX Tablets are red and contain 400 mg of active drug.

- Minor editorial changes to the package insert were also made.

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number	Date Submitted	Date Received
AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg	NDA 21-085	S-014	September 30, 2002	October 1, 2002
		S-017	January 28, 2003	January 30, 2003
AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V.	NDA 21-277	S-006	September 30, 2002	October 1, 2002
		S-009	January 28, 2003	January 30, 2003

These supplemental applications, submitted as “Supplement- Changes Being Effectuated,” provide for the following changes to the labeling:

Double underline=added text

~~Strikethrough~~=deleted text

Package Insert:

- **WARNINGS Section:**

~~“Although not observed in clinical trials, Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with quinolones, including moxifloxacin.”~~

- **PRECAUTIONS, Drug Interactions, Warfarin sub-section:**

Warfarin: No significant effect of moxifloxacin on R- and S-warfarin was detected in a clinical study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in the presence of moxifloxacin. ~~However, since some Quinolones, including moxifloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity.;~~ Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone ~~antimicrobial~~ is administered concomitantly with warfarin or its derivatives.

- **ADVERSE REACTIONS, Additional clinically relevant uncommon events:**

~~“DIGESTIVE: vomiting, abnormal liver function test, dyspepsia, dry mouth, constipation, oral moniliasis, anorexia, stomatitis, glossitis, flatulence, gastrointestinal disorder, cholestatic jaundice, GGTP increased”~~

- **ADVERSE REACTIONS, Additional clinically relevant rare events:**

~~“abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation, convulsions, depersonalization, depression, diarrhea (*Clostridium difficile*), dysphagia, ECG abnormal, emotional lability, face edema, gastritis, hallucinations, hyperglycemia, hyperlipidemia, hypertonia, hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic), kidney function abnormal, parosmia, pelvic pain, prothrombin increase, sleep disorders, speech disorders, supraventricular tachycardia, taste loss, tendon disorder, thinking abnormal, thromboplastin decrease, tinnitus, tongue discoloration, urticaria, vasodilatation, ventricular tachycardia”~~

- **ADVERSE REACTIONS, Post-Marketing Adverse Event Reports sub-section:**

Additional adverse events reported from worldwide post-marketing experience with moxifloxacin include anaphylactic reaction, anaphylactic shock, hepatitis (predominantly cholestatic), pseudomembranous colitis, psychotic reaction, Stevens-Johnson syndrome, syncope, and tendon rupture.

- **DOSAGE AND ADMINISTRATION**

Preparation for administration of AVELOX I.V. injection premix in flexible containers:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin from an appropriate transfer set (e.g. one that does not require excessive force, such as ISO compatible administration set) into port with a gentle twisting motion until pin is firmly seated.

NOTE: Refer to complete directions that have been provided with the administration set.

- **Patient Information About: AVELOX® Section:**

### **Who should not take Avelox?**

You should not take AVELOX if you have ever had a severe allergic reaction to any of the group of antibiotics known as “quinolones” such as ciprofloxacin or levofloxacin. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking AVELOX and call your healthcare professional.

### **What are the possible side effects of AVELOX?**

AVELOX is generally well tolerated. The most common side effects caused by AVELOX, which are usually mild, include dizziness, nausea, and diarrhea and dizziness. If diarrhea persists call your healthcare provider. 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 7,900 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.

Convulsions have been reported in patients receiving quinolone antibiotics. Be sure to let your physician know if you have a history of convulsions. Quinolones, including AVELOX, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

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 healthcare professional.

### **Remember**

For more complete information about AVELOX request full prescribing information from your healthcare professional, pharmacist, or visit our website at [www.aveloxusa.com](http://www.aveloxusa.com).

- Minor editorial changes to the package insert were also made.

Flexibag and Overwrap:

- The following statement was added to the flexibag and overwrap. :

Insert piercing pin from an appropriate transfer set (e.g. one that does not require excessive force, such as ISO compatible administration set) into port with a gentle twisting motion until pin is firmly seated.

We have 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.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted February 26, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case 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, these submissions should be designated "FPL for approved supplement NDA 21-085/S-014, S-015, S-017 and NDA 21-277/S-006, S-007, S-009." Approval of these submissions by the FDA is not required before the labeling is used.

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third

party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to a NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to a NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for the addition of penicillin-resistant *Streptococcus pneumoniae* to the Community Acquired Pneumonia indication for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

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, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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 any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.

Director

Division of Special Pathogen and Immunologic Drug  
Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

Enclosure (labeling)



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

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Renata Albrecht  
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