



DEC 15 1999

TRANSMITTED VIA FACSIMILE

Martina Ziska, MD, PhD
Deputy Director, Regulatory Affairs
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

RE: **NDA # 21-085**
Avelox (moxifloxacin hydrochloride) Tablets
MACMIS # 8577

Dear Dr. Ziska,

As part of our routine monitoring and surveillance activities, it has come to the attention of the Division of Drug Marketing, Advertising, and Communications that Bayer Corporation is promoting its product, Avelox, in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, we refer to a press release issued by Bayer on December 13, 1999. We request that Bayer cease dissemination of false and/or misleading messages in all promotional activities as outlined below.

Background

Avelox is a newly approved fluoroquinolone antibiotic, approved for treatment of adults (≥ 18 years of age) with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and community acquired pneumonia caused by susceptible organisms as listed in the product labeling. The approved product labeling for Avelox carries a bolded warning describing a significant cardiac hazard associated with the use of Avelox. Specifically, Avelox 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 (insufficient blood potassium levels), and patients receiving certain commonly prescribed antiarrhythmic agents (quinidine, procainamide, amiodarone, sotalol). Furthermore, the drug should be used with caution when given concurrently with other drugs that prolong the QT interval, since an additive effect of Avelox and these drugs cannot be excluded. QT prolongation may lead to an increased risk for ventricular arrhythmias, a serious condition.

Lack of fair balance and presentation of misleading safety information

In its press release, Bayer failed to provide sufficient information relating to this bolded warning, thereby undermining the effective communication of this important risk information. Bayer's presentation of the warning using complex medical terminology does not effectively communicate either the nature or seriousness of the risk to a consumer audience. Furthermore, Bayer stated that the reason for the warning was that Avelox had not been studied in certain populations, but failed to mention that this adverse effect had actually occurred in some patients. Also, unlike Bayer's very detailed claim that Avelox can be taken with many other medications in which they specifically list all the drugs, Bayer's presentation of the bolded warning is so vague as to be ineffective.

Bayer's presentation regarding drug interactions is misleading in that it fails to reveal facts material with respect to consequences associated with the drug. Bayer suggests that Avelox has no significant drug interactions with many commonly prescribed medications. However, they fail to mention that an additive effect of Avelox and drugs that prolong the QT interval, such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants, cannot be excluded, and therefore Avelox should be used with caution when given concurrently with these drugs. In addition, Bayer fails to mention that Avelox does have a potential drug interaction with another very commonly prescribed class of medications, the nonsteroidal anti-inflammatory drugs (NSAIDs). Furthermore, although no significant effect of moxifloxacin on warfarin was detected in a small clinical study, the approved product labeling does caution that prothrombin time should be closely monitored (to detect any enhanced anticoagulant effect) if a quinolone antimicrobial (like moxifloxacin) is concomitantly administered with warfarin. Bayer fails to include this information to balance their drug interaction claim.

Promotion of unapproved uses

Bayer's press release suggests that Avelox is effective against resistant pathogens, and/or that Avelox addresses the problem of rising bacterial resistance. Examples include, but are not limited to, the following statements:

- "Physicians welcome new advance in fight against respiratory tract infections, rising bacterial resistance;"
- "Many of the pathogens responsible for these infections have developed resistance to the most commonly prescribed antibiotics, creating a real and very immediate need for new agents to fill the void;"
- "Respiratory tract infections can lead to serious health consequences and the organisms that cause these infections are becoming more difficult to treat."

Bayer has not provided substantial evidence to support the use of Avelox against resistant pathogens. Therefore, these suggestions and implications constitute promotion of an unapproved use.

Unsubstantiated superiority claims

Bayer claims that Avelox is a new advance in treating respiratory tract infections, suggesting that Avelox has been shown to be superior to other antibiotics. This claim is unsubstantiated and misleading.

Bayer also claims, "Avelox does not cause photosensitivity or serious liver toxicity in patients, unlike many other antibiotics." This is an unsubstantiated superior safety claim. Also, this claim is inconsistent with the approved product labeling which states that, although rare, abnormal liver elevations did occur in some patients.

Bayer should immediately cease dissemination of these and similar claims and presentations in all promotional materials for Avelox. Bayer should submit a written response indicating its intent to comply no later than December 29, 1999. Bayer's response should include a list of materials that will be discontinued, with their discontinuation date. Your response should be directed to Jo Ann Spearmon, Pharm.D., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Room 17B-20, 5600 Fishers Lane, Rockville, Maryland 20857. We remind Bayer that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS # 8577, in addition to the NDA number.

Sincerely,

/s/

Tracy Acker, Pharm.D.
Branch Chief (Acting)
Division of Drug Marketing,
Advertising, and Communications

Printed by []
Electronic Mail Message

Date: 13-Dec-1999 02:35pm

From:

Dept:

Tel No:

Subject: Bayer press release

For Immediate Release

FDA APPROVES AVELOX™ (moxifloxacin hydrochloride), AN IMPORTANT NEW TREATMENT FOR RESPIRATORY ILLNESSES

Physicians Welcome New Advance in Fight Against Respiratory Tract Infections, Rising Bacterial Resistance

West Haven, CT, December 13, 1999 -- The U.S. Food and Drug Administration has approved Avelox™, a new highly effective, once-a-day antibiotic indicated for the treatment of common respiratory tract infections (RTI), including acute bacterial exacerbations of chronic bronchitis (ABECB), community-acquired pneumonia of mild to moderate severity (CAP) and acute bacterial sinusitis,* Bayer Corporation, Pharmaceutical Division today announced.

A New Advance for Treating Respiratory Tract Infections

"We are very pleased that the FDA has recognized the value of Avelox™ for the treatment of many common community-acquired respiratory tract infections," said Lawrence E. Posner, MD, senior vice president, pharmaceutical development, Bayer Corporation, Pharmaceutical Division. "Many of the pathogens responsible for these infections have developed resistance to the most commonly prescribed antibiotics, creating a real and very immediate need for new agents to fill the void."

In laboratory studies and clinical trials, Avelox™ was shown to be effective against common respiratory pathogens, including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis, and atypicals such as Chlamydia pneumoniae and Mycoplasma pneumoniae. The recommended therapeutic dose for Avelox™ is 400 mg taken once daily for five or 10 days, depending on the specific infection: five days for ABECB and 10 days for CAP and acute bacterial sinusitis.

"Respiratory tract infections can lead to serious health consequences and the organisms that cause these infections are becoming more difficult to treat," said David Talan, M.D., Chairman of the Department of Emergency Medicine at Olive View-UCLA Medical Center. "Avelox™ will be a highly useful addition to physicians' fight against these common respiratory tract infections, especially as we seek more potent therapies that allow confidence in treating patients as out-patients," Dr. Talan said.

Safety Profile

Based on clinical trials involving nearly 8,000 patients, Avelox™ is safe and well tolerated. In addition, the trials demonstrate that Avelox™ does not cause photosensitivity (sensitivity to light) or serious liver toxicity in patients, unlike many other antibiotics.

Unlike many widely used antibiotics, Avelox™ is not metabolized by the enzyme system (cytochrome P450) that breaks down many other drugs and, therefore, can be safely taken with a wide array of other medications. Avelox™ did not trigger any clinically significant interactions with

theophylline, warfarin, digoxin, probenecid, ranitidine, or glyburide, all commonly prescribed medications. Additionally, no interactions between Avelox and food were seen during the clinical trials.

Further, because it has a half-life of 12 to 14 hours, Avelox™ has the added advantage of not having to be taken at any particular time, nor does it need to be taken along with meals. In addition, no dosage adjustments are required based on age, race or gender. During extensive clinical trials the most common adverse reactions were nausea and diarrhea and were described as only mild to moderate in severity and required no treatment.

Avelox™ is contraindicated in patients with a known hypersensitivity to moxifloxacin or any quinolone antimicrobial.

The safety and efficacy of Avelox™ in pediatric patients below the age of 18 and in pregnant or lactating women have not been established.

Avelox™ should be avoided in patients with known prolongation of the QTc interval, in patients taking QTc interval-prolonging drugs, and in patients with uncorrected hypokalemia, because it has not been studied in these populations.

As with other quinolones, Avelox™ should be used with caution in patients with known or suspected central nervous system disorders or patients who have a predisposition to seizures. As with other quinolones, aluminum or magnesium-based antacids, multivitamins containing iron or zinc, or sucralfate should only be administered four hours before or eight hours after taking Avelox.™

Bayer Corporation

Bayer Corporation is a research-based company with major businesses in health care and life sciences and chemicals. The company had 1998 sales of \$8.1 billion and employs more than 23,000 people. Bayer Corporation is investing \$15 billion in capital expenditures and research and development from 1995 through the year 2004. 1999 capital investment and R&D expenditures are projected to total \$1.6 billion. Bayer Corporation, with headquarters in Pittsburgh, is a member of the worldwide Bayer Group, a \$31 billion international life sciences, polymers and specialty chemicals group based in Leverkusen, Germany.

* Due to susceptible pathogens.

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