Bayer HealthCare Pharmaceuticals

IMPORTANT DRUG WARNING

October 22, 2008

Subject: **Important Change in the Avelox® (moxifloxacin hydrochloride) and Cipro® (ciprofloxacin) Complete Prescribing Information – Addition of Boxed Warning and Medication Guide Regarding Tendinitis and Tendon Rupture**

Dear Health Care Professional:

Bayer HealthCare Pharmaceuticals Inc. would like to inform you of important changes to the prescribing information for fluoroquinolone antibiotics for systemic use in the United States, including all formulations of Avelox® (moxifloxacin hydrochloride) and Cipro® (ciprofloxacin).

To reinforce the warning information that is already included in the prescribing information for fluoroquinolone antibiotics, the U.S. Food and Drug Administration (FDA) has requested that all license holders of these products, including Bayer, implement a class label change for a Boxed Warning for tendinitis and tendon rupture, and develop a Risk Evaluation Mitigation Strategy (REMS), which includes a Medication Guide for patients describing the important adverse events associated with fluoroquinolones.

To ensure that you and your patients are fully informed about these potential risks, the WARNINGS sections of the product labeling for all fluoroquinolone antibiotics, including Avelox® and Cipro® , have been updated to include the following BOXED WARNING:

WARNING:
Fluoroquinolones, including AVELOX®/CIPRO®, 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).

You should consider these potential risks when prescribing fluoroquinolones and report any serious adverse events. Please advise your patients, at the first sign of tendon pain, swelling or inflammation, to stop taking the fluoroquinolone, to avoid exercise and use of the affected area, and to promptly contact you about changing to a non-fluoroquinolone antibiotic. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported.

The Patient Package Inserts for all fluoroquinolones including Avelox® and Cipro® have been replaced with Medication Guides. Patients should be advised to read the Medication Guide before beginning therapy. In addition to the Boxed Warning and the Medication Guide, the following additional changes have been made to the labeling:

1. The **WARNINGS/Tendon Effects** subsections of both the Avelox® and Cipro® product labels were renamed "**Tendinopathy and Tendon Rupture**", moved to the first paragraph of the **WARNINGS** sections, and updated as follows:

   Tendinopathy and Tendon Rupture: Fluoroquinolones, including AVELOX/CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture 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. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. AVELOX/CIPRO should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

2. The information on tendon adverse reactions in the **PRECAUTIONS/Information for Patients** subsections of the labeling for both products was moved to the first bullet and updated as follows:

   - to 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/CIPRO 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.

3. The information on tendon adverse events in the **PRECAUTIONS/Geriatric Use** subsection of the labeling for both products was moved to the first paragraph and updated as follows:

   Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as AVELOX/CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing AVELOX/CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue AVELOX/CIPRO and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

Our highest priority is patient safety. Bayer HealthCare continuously monitors safety reports of all of its medicines and regularly provides this information to global regulatory authorities, including the FDA.

Bayer HealthCare is the license holder for Avelox® and Cipro®. Under terms of a marketing agreement, Schering-Plough markets these products in the United States. Bayer will post this information for health care professionals and patients on www.pharma.bayer.com, www.avelox.com and www.cipro.com.

Please refer to the accompanying Important Information about Avelox® and Cipro® and the enclosed Avelox® and Cipro® complete Prescribing Information.

If you wish to request further information, please contact Schering-Plough Global Medical Information at 1-800-526-4099.

Sincerely,

Paul MacCarthy, MD, FRCPI
Vice President, Head US Medical Affairs

Important Information About Avelox® (moxifloxacin hydrochloride) and Cipro® (ciprofloxacin)

Indication (Avelox® and Cipro®):
Avelox® and **Cipro®** are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed in the ***enclosed Prescribing Information.***

Safety Information:
In addition to tendon ruptures (discussed above), other side effects that are associated with fluoroquinolone use that are included in the **WARNINGS** or **PRECAUTIONS** sections of the **Avelox®** and **Cipro®** labeling include:

- *Anaphylactic and serious allergic reactions.* These may occur even following a single dose. Serious dermatologic reactions such as Stevens Johnson Syndrome or Toxic Epidermal Necrolysis may also occur.
- *Neurologic Events, including CNS Effects, Peripheral neuropathy*. CNS effects, including convulsions, hallucinations, restlessness, tremors, anxiety, confusion, depression, and insomnia may occur after the first dose. These drugs should be used with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold. Fluoroquinolones have been associated with rare cases of sensory or sensorimotor axonal peripheral neuropathy, which may be irreversible.
- *QTc prolongation and rarely, torsade de pointes.* Fluoroquinolones should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected electrolyte disorders and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic agents. This potential risk may be increased with concomitant use of cisapride, erythromycin, antipsychotics and tricyclic antidepressants.
- *Clostridium difficile associated diarrhea* (CDAD). CDAD has been reported with the use of nearly of all antibacterial agents, including fluoroquinolones, and may range in severity from mild diarrhea to fatal colitis. Patients should be counseled that CDAD can present with watery or bloody stools (with or without stomach cramps and fever), may occur sometimes as late as two or more months after fluoroquinolone treatment, and should be evaluated by a health care provider.
- Rarely, damage to the liver, kidneys or bone marrow; alterations in glucose homeostasis, and phototoxicity may occur.