



**IMPORTANT
DRUG
WARNING**

March 30, 2011

Subject: Important Changes in the Avelox® (moxifloxacin hydrochloride) and Cipro® (ciprofloxacin) Complete Prescribing Information – Addition of Boxed Warning and Change to Product Label and Medication Guide Regarding Myasthenia Gravis Exacerbation

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 myasthenia gravis exacerbation and a modification to the Risk Evaluation Mitigation Strategy (REMS), including the Medication Guide for patients that describes the important adverse events associated with fluoroquinolones. The FDA requested revisions to the prescribing information as they became aware of fluoroquinolone-associated myasthenia gravis exacerbation, which is a potentially life-threatening event and may require ventilatory support. This was based on review of post-marketing adverse events from the Adverse Event Reporting System (AERS) and published case reports in the scientific literature.

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 additional text in blue and underlined in 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 and Precautions).

Fluoroquinolones, including AVELOX®/CIPRO®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid AVELOX®/CIPRO® in patients with known history of myasthenia gravis (See Warnings and Precautions).

You should consider these potential risks when prescribing fluoroquinolones and report any serious adverse events. Please advise your patients that fluoroquinolones like AVELOX®/CIPRO® may cause

worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should promptly contact you if they have any worsening muscle weakness or breathing problems.

In addition to the change to the Boxed Warning for AVELOX® and CIPRO®, the following additional changes have been made to the labeling:

1. The following sub-section was added to the **WARNINGS** subsection of the CIPRO® product label and the **WARNINGS AND PRECAUTIONS** section of the AVELOX® product label were updated as follows:

Exacerbation of myasthenia gravis

Fluoroquinolones, including AVELOX®/CIPRO®, 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®/CIPRO® in patients with known history of myasthenia gravis.

2. The **PRECAUTIONS/Information for Patients** subsections of the CIPRO® product label and the **Serious and Potentially Serious Adverse Reactions** section for the AVELOX® product label were updated as follows:

- Fluoroquinolones like AVELOX®/CIPRO® 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.

3. The **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports** section for the CIPRO® product label was updated as follows:

- exacerbation of myasthenia gravis

Patients should be advised to read the Medication Guide before beginning therapy. The following changes have been made to the Medication Guide:

1. The section “**What is the most important information I should know about AVELOX®/CIPRO®**” of the Medication Guide was updated as follows:

- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like AVELOX®/CIPRO® 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.
- To tell your healthcare provider about all your medical conditions, including if you have a disease that causes muscle weakness (myasthenia gravis) was added to the “**What should I tell my healthcare provider before taking AVELOX®/CIPRO®**”, see **What is the most important information I should know about AVELOX®/CIPRO®** section of the Medication Guide.

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

To report new cases of exacerbation of myasthenia gravis or other adverse reactions, please contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or to request further information on AVELOX®/CIPRO®, please contact Merck National Service Center at 1-800-526-4099.

Alternatively, adverse events may be reported to FDA’s MedWatch reporting system:

- By phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178),
- Online www.fda.gov/medwatch/report.htm or
- Mailed, using the MedWatch for FDA 3500 postage paid form, to the FDA Safety Information and Adverse Event Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787

Please refer to the accompanying Important Information about AVELOX® and CIPRO® for the complete indication and other important risks. Please also see the enclosed Prescribing Information, including BOXED WARNINGS and Medication Guide for AVELOX® and CIPRO®.

If you wish to request further information, please contact Merck National Service Center at 1-800-526-4099.

Sincerely,



Pamela A. Cyrus, M.D.
Vice President and Head of U.S. Medical Affairs

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

Indication (Avelox® and Cipro®):

Avelox® and **Cipro®** are indicated for the treatment of following infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below.

Avelox® (Tablets and I.V.) is indicated for the treatment of the following infections:

- **Acute Bacterial Sinusitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*
- **Acute Bacterial Exacerbation of Chronic Bronchitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, or *Moraxella catarrhalis*
- **Community Acquired Pneumonia** caused by *Streptococcus pneumoniae* (including multi-drug resistant strains*), *Haemophilus influenzae*, *Moraxella catarrhalis*, methicillin-susceptible *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*
* MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (minimum inhibitory concentrations [MIC] ≥ 2 mcg/mL), 2nd generation cephalosporins (for example, cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole
- **Uncomplicated Skin and Skin Structure Infections** caused by methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*
- **Complicated Skin and Skin Structure Infections** caused by methicillin-susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae*
- **Complicated Intra-Abdominal Infections** including polymicrobial infections such as abscess caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides thetaiotaomicron*, or *Peptostreptococcus species*

CIPRO® Tablets and Oral Suspension are indicated for the treatment of the following infections:

Adult Patients:

- **Urinary Tract Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*
- **Acute Uncomplicated Cystitis in females** caused by *Escherichia coli* or *Staphylococcus saprophyticus*
- **Chronic Bacterial Prostatitis** caused by *Escherichia coli* or *Proteus mirabilis*
- **Lower Respiratory Tract Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or penicillin-susceptible *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis. NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*
- **Acute Sinusitis** caused by *Haemophilus influenzae*, penicillin-susceptible *Streptococcus pneumoniae*, or *Moraxella catarrhalis*
- **Skin and Skin Structure Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus epidermidis*, or *Streptococcus pyogenes*
- **Bone and Joint Infections** caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*
- **Complicated Intra-Abdominal Infections** (used in combination with metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*
- **Infectious Diarrhea** caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei* when antibacterial therapy is indicated
- **Typhoid Fever (Enteric Fever)** caused by *Salmonella typhi*.
NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated
- **Uncomplicated cervical and urethral gonorrhea** due to *Neisseria gonorrhoeae*

Pediatric patients (1 to 17 years of age):

- **Complicated Urinary Tract Infections and Pyelonephritis** due to *Escherichia coli*. NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues

Adult and Pediatric Patients:

- **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*

CIPRO® I.V. is indicated for the treatment of the following infections:

Adult Patients:

- **Urinary Tract Infections** caused by *Escherichia coli* (including cases with secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*
- **Lower Respiratory Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae* subspecies *pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or penicillin-susceptible *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*
- **Nosocomial Pneumonia** caused by *Haemophilus influenzae* or *Klebsiella pneumoniae*
- **Skin and Skin Structure Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae* subspecies *pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus epidermidis*, or *Streptococcus pyogenes*
- **Bone and Joint Infections** caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*
- **Complicated Intra-Abdominal Infections** (used in conjunction with metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*
- **Acute Sinusitis** caused by *Haemophilus influenzae*, penicillin-susceptible *Streptococcus pneumoniae*, or *Moraxella catarrhalis*
- **Chronic Bacterial Prostatitis** caused by *Escherichia coli* or *Proteus mirabilis*
- **Empirical Therapy for Febrile Neutropenic Patients** in combination with piperacillin sodium

Pediatric patients (1 to 17 years of age):

- **Complicated Urinary Tract Infections and Pyelonephritis** due to *Escherichia coli*.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.

Adult and Pediatric Patients:

- **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

CIPRO® XR is indicated for the treatment of the following infections:

- **Uncomplicated Urinary Tract Infections (Acute Cystitis)** caused by *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, or *Staphylococcus saprophyticus*
- **Complicated Urinary Tract Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*
- **Acute Uncomplicated Pyelonephritis** caused by *Escherichia coli*

Selected Safety Information:

In addition to exacerbation of myasthenia gravis (discussed above), below are some of the other side effects that are associated with fluoroquinolone use that are included in the **WARNINGS** or **PRECAUTIONS** sections of the **AVELOX**[®] and **CIPRO**[®] labeling. Please refer to the enclosed Prescribing Information for complete safety information.

- *Tendinopathy and Tendon Rupture.* Fluoroquinolones, including AVELOX/CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. 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
- *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 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 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.
- Damage to the liver, kidneys or bone marrow; alterations in glucose homeostasis, and phototoxicity may occur.