



November 2008

Subject: Important Change in the LEVAQUIN® (levofloxacin) Complete Prescribing Information – Addition of Boxed Warning and Medication Guide Regarding Tendinitis and Tendon Rupture

Dear Healthcare Professional:

PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc, would like to inform you of important changes to the prescribing information for LEVAQUIN® (levofloxacin) tablet, oral solution, and injectable formulations.

The LEVAQUIN® labeling has been updated to include a **BOXED WARNING** (see below), as well as additional information in **5.1 WARNINGS AND PRECAUTIONS/Tendinopathy and Tendon Rupture**. Information on tendon effects, including tendon ruptures, also appears in **8.5 USE IN SPECIFIC POPULATIONS/Geriatric Use**. In addition, a **patient Medication Guide** has been added in section 17.5 of the LEVAQUIN® labeling.

The BOXED WARNING reads as follows:

WARNING:
Fluoroquinolones, including LEVAQUIN®, 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)].

The revised **WARNINGS AND PRECAUTIONS/Tendinopathy and Tendon Rupture** information reads as follows:

5.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including LEVAQUIN®, 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 those 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 been reported 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. LEVAQUIN® 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. [see *Adverse Reactions (6.3); Patient Counseling Information (17.3)*].

Healthcare professionals should report all serious adverse events to 1-800-526-7736 or to FDA's MedWatch Adverse Event Reporting program online (at www.fda.gov/MedWatch/report.htm), by facsimile (1-800-FDA-0178), by telephone (1-800-FDA-1088), or by returning the postage-paid FDA form 3500 (which may be downloaded from www.fda.gov/MedWatch/getforms.htm) by mail (to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787).

For medical inquiries, please call the Customer Communications Center at 1-800-526-7736 or contact your PriCara® representative.

Please refer to pages 3-4 for the indications and additional important safety information for LEVAQUIN® (levofloxacin) and read the enclosed revised package insert for complete prescribing information for LEVAQUIN® or visit <http://www.levaquin360.com>.

Sincerely,



Norman Rosenthal, MD
Vice President, Medical Affairs

Important Information About LEVAQUIN® (levofloxacin)

Indication

LEVAQUIN® is indicated in adults 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.

Additional Important Safety Information

In addition to tendon ruptures (discussed above), other side effects that are associated with fluoroquinolone use that are included in the **WARNINGS and PRECAUTIONS** section of the LEVAQUIN® labeling include:

Levofloxacin is contraindicated in persons with known hypersensitivity to levofloxacin or other quinolone antibacterials. Serious and occasionally fatal events, such as hypersensitivity and/or anaphylactic reactions and some of unknown etiology, have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions may include effects on the liver, including hepatitis, jaundice, and acute hepatic necrosis or failure, and hematologic effects, including agranulocytosis, thrombocytopenia, and other hematologic abnormalities. These reactions may occur following the first dose or multiple doses. Discontinue levofloxacin at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity.

Severe hepatotoxicity (including acute hepatitis and fatal events) not associated with hypersensitivity has also been reported. Discontinue immediately if signs and symptoms of hepatitis develop.

Central nervous system effects, including convulsions, confusion, anxiety, depression, and insomnia, may occur after the first dose. As with other quinolones, levofloxacin should be used with caution in patients with known or suspected central nervous system disorders that may predispose them to seizures or lower the seizure threshold.

Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including levofloxacin. If diarrhea occurs, evaluate for CDAD and treat appropriately.

Rare cases of peripheral neuropathy have been reported in patients receiving quinolones, including levofloxacin. Discontinue if symptoms of neuropathy occur to prevent the development of an irreversible condition.

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval, infrequent cases of arrhythmia, and rare cases of torsades de pointes. Levofloxacin should be avoided in patients with known risk factors such as prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

Moderate to severe photosensitivity/phototoxicity reactions can be associated with the use of quinolones after sun or UV light exposure. Blood glucose disturbances

have been reported with use of quinolones, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent or with insulin.

Safety and efficacy in pregnant women and nursing mothers have not been established. The risk-benefit assessment indicates that levofloxacin is only appropriate in pediatric patients for treatment of inhalational anthrax (post-exposure). The safety in pediatric patients treated for more than 14 days has not been studied.

Antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or Videx^{®*} (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, should not be taken within 2 hours before or after levofloxacin administration.

The most common adverse drug reactions ($\geq 3\%$) in US clinical trials were nausea, headache, diarrhea, insomnia, constipation, and dizziness.

* Videx is a registered trademark of Bristol-Myers Squibb Company.