



NDA 20-634/S-045
NDA 20-635/S-048
NDA 21-721/S-013

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, LLC
Attention: Ms. Cynthia Chianese
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Chianese:

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

NDA #	Drug Product	Supplement Number	Date of supplement	Date of receipt
20-634	Levaquin® (levofloxacin) Tablets 250 mg, 500 mg, and 750 mg	045	April 30, 2007	May 1, 2007
20-635	Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection, 5mg/mL	048	April 30, 2007	May 1, 2007
21-721	Levaquin® (levofloxacin) Oral Solution, 25 mg/mL	031	April 30, 2007	May 1, 2007

These “Changes Being Effected” supplemental new drug applications provide for the following revisions to the package insert for Levaquin® to ensure consistency in the communication of the risks of acute liver failure and acute severe liver injury, QTc prolongation/torsades de pointes, tendon rupture, and toxic epidermal necrolysis (TEN), submitted in response to the Supplement Request letter issued by the Division on May 19, 2006.

The supplemental applications provide for revisions as follows (additions are underline and deletions are ~~strikethrough~~):

1. In the **WARNINGS** section, the fifth paragraph regarding hypersensitivity was replaced with the underlined text below to provide greater clarity in the grouping of hypersensitivity findings, and a section heading of **Hypersensitivity Reactions** was added before the fourth paragraph. The text of this subsection reads as follows:

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated (See **PRECAUTIONS** and **ADVERSE REACTIONS**).

~~Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**.)~~

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including Levaquin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis;
- pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS/ Information for Patients** and **ADVERSE REACTIONS**).

2. The **WARNINGS/Tendon Effects** subsection was modified as follows:

Ruptures of the shoulder, hand, Achilles tendon, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk ~~may be~~ is increased in patients receiving concomitant corticosteroids, especially the elderly.

3. The **PRECAUTIONS/Information for Patients** subsection was modified as follows:

- to discontinue LEVAQUIN treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been ~~confidently~~ excluded. The risk of serious tendon disorders is higher in those over 65 years of age, especially those on steroids.

4. The following text was added to the **PRECAUTIONS/Information for Patients** subsection following the last bulleted point:

- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QTc interval, including prolonged heart palpitations or a loss of consciousness.

5. Under the **PRECAUTIONS/Geriatric Use** subsection, the following paragraph was included after the current second paragraph in the labeling:

Patients over 65 are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as LEVAQUIN. This risk is further increased with age concomitant steroid therapy. Tendon rupture usually involves the Achilles, hand or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing levofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.

6. Under the **ADVERSE REACTIONS/Post-Marketing Adverse Reactions** subsection, the following event was included:

- a. hepatic failure (including fatal cases)

7. In the **“Patient Package Insert,”** the following paragraphs were added under the subsection, **“What are possible side effects of Levaquin?”**:

Pain, swelling, and tears of Achilles, Ruptures of shoulder, or hand, or Achilles tendons have been reported in patients receiving fluoroquinolones, including LEVAQUIN, The risk

for tendon effects is higher if you are over 65 years old, and especially if you are taking corticosteroids. If you develop pain, swelling, or rupture of a tendon you should stop taking LEVAQUIN, avoid exercise and strenuous use of the affected area, and contact your health care professional provider.

In a few people, LEVAQUIN, like some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. The rare heart problem is called QT prolongation and can cause an abnormal heartbeat and can be very dangerous. The chances of this event are increased in those with a family history of prolonged QT interval, low potassium (hypokalemia), and who are taking drugs to control heart rhythm, called class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. You should call your healthcare provider right away if you have any prolonged heart palpitations (a change in the way your heart beats) or a loss of consciousness (fainting spells).

We 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.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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

Renata Albrecht
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