DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634/S-051
NDA 20-635/S-055
NDA 21-721/S-019

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
ATTN: Ms. Alysia Baldwin-Ferro
Senior Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Baldwin-Ferro:

Please refer to your supplemental new drug applications dated November 9, 2007, received on November 13, 2007, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Product
20-634	051	Levaquin® (levofloxacin) Tablets, 250 mg, 500 mg, and 750 mg
20-635	055	Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection, 5 mg/mL
21-721	019	Levaquin® (levofloxacin) Oral Solution, 25 mg/mL

We acknowledge receipt of your submissions dated February 14, 2008, March 6, 2008 (2), March 19, 2008, April 1, 2008, and April 15, 2008:

These "Special Supplements - Changes Being Effected" supplemental applications propose revising information pertaining to hepatotoxicity throughout the labeling for the package insert of Levaquin.

We have 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. The final printed labeling (FPL) must be identical the content of labeling for the package insert and patient package insert submitted on April 15, 2008.

The revisions to the package insert were as follows (additions are noted with underline and deletions noted with ~~strikethrough~~):

1. The second and third bullets of the **HIGHLIGHTS/WARNINGS AND PRECAUTIONS** subsection of the package insert were revised as follows:

   - ~~Liver, h~~ Hematologic (including agranulocytosis, thrombocytopenia)~~,~~ and renal toxicities may occur after multiple doses (5.2)
   - Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur (5.3)

2. The **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS/Geriatrics** subsection was revised as follows:

   Geriatrics: Severe hepatotoxicity has been reported (5.3, 8.5, 17). The majority of reports describe patients 65 years of age or older. May have increased risk of tendon disorders (including rupture), especially with concomitant corticosteroid use (5.4, 8.5, 17). May be more susceptible to prolongation of the QT interval. (5.8, 8.5, 17).

3. The **FULL PRESCRIBING INFORMATION/5. WARNINGS AND PRECAUTIONS/5.3 Hepatotoxicity** subsection was added to the package insert as follows:

   5.3 Hepatotoxicity

   Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with LEVAQUIN®. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity were not associated with hypersensitivity [see Warnings and Precautions (5.2)]. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. LEVAQUIN® should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see Adverse Reactions (6); Patient Counseling Information (17.3)].

4. The **FULL PRESCRIBING INFORMATION/6. ADVERSE REACTIONS/6.1 Serious and Otherwise Important Adverse Reactions** subsection of the package insert was revised as follows:

   6.1 Serious and Otherwise Important Adverse Reactions

   The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

   - Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
   - Other Serious and Sometimes Fatal Reactions *[see Warnings and Precautions (5.2)]*
   - Hepatotoxicity *[see Warnings and Precautions (5.3)]*
   - Tendon Effects *[see Warnings and Precautions (5.4)]*
   - Central Nervous System Effects *[see Warnings and Precautions (5.5)]*
   - *Clostridium difficile*-Associated Diarrhea *[see Warnings and Precautions (5.6)]*

- Peripheral Neuropathy *[see Warnings and Precautions (5.7)]*
- Prolongation of the QT Interval *[see Warnings and Precautions (5.8)]*
- Musculoskeletal Disorders in Pediatric Patients *[see Warnings and Precautions (5.9)]*
- Blood Glucose Disturbances *[see Warnings and Precautions (5.10)]*
- Photosensitivity/Phototoxicity *[see Warnings and Precautions (5.11)]*
- Development of Drug Resistant Bacteria *[see Warnings and Precautions (5.12)]*

5. The **FULL PRESCRIBING INFORMATION/8. USE IN SPECIFIC POPULATIONS/8.5 Geriatric Use** subsection of the package insert has been revised as follows:

In phase 3 clinical trials, 1,945 LEVAQUIN®-treated patients (26%) were ≥ 65 years of age. Of these, 1,081 patients (14%) were between the ages of 65 and 74 and 864 patients (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with LEVAQUIN®. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. LEVAQUIN® should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Warnings and Precautions (5.3)]*.

~~Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using LEVAQUIN® with concomitant drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia)~~ *[see Warnings and Precautions]*.

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 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 LEVAQUIN® 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 *[see Warnings and Precautions (5.4)]*.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using LEVAQUIN® with concomitant drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) *[see Warnings and Precautions (5.8)]*.

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However, since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Clinical Pharmacology (12.3)]*.

6. Another bullet for hepatotoxicity was added to the **FULL PRESCRIBING INFORMATION/ 17. PATIENT COUNSELING INFORMATION/17.3 Serious and Potentially Serious Adverse Reactions** section as follows:

   Patients should be informed of the following serious adverse reactions that have been associated with LEVAQUIN® or other quinolone use:

   - **Hepatotoxicity:** Severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking LEVAQUIN®. Patients should inform their physician and be instructed to discontinue LEVAQUIN® treatment immediately if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.

7. A paragraph was added to the **FULL PRESCRIBING INFORMATION/17. PATIENT COUNSELING INFORMATION/17.5 FDA-Approved Patient Labeling/Patient Information About Levaquin/What are possible side effects of Levaquin?** subsection as follows:

   Hepatotoxicity (liver damage) has been reported in patients receiving LEVAQUIN®. Call your doctor right away if you have unexplained symptoms such as: nausea or vomiting, stomach pain, fever, weakness, abdominal pain or tenderness, itching, unusual or unexplained tiredness, loss of appetite, light colored bowel movements, dark colored urine or yellowing of your skin or the whites of your eyes.

8. Editorial changes throughout the labeling were made to correct numbering, links, organization, and formatting.

CONTENT OF LABELING

As soon as possible, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "**SPL for approved NDA 20-634/S-051, NDA 20-635/S-055, and NDA 21-721/S-019**."

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

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

REPORTING REQUIREMENTS

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, call Rebecca D. Saville, Pharm.D., Regulatory 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 this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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