DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634/S-044
NDA 20-635/S-047
NDA 21-721/S-012

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
ATTN: Ms. Cynthia Chianese
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, N.J. 08560-0200

Dear Ms. Chianese:

Please refer to your supplemental new drug applications, dated and received on January 31, 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	044	Levaquin® (levofloxacin) Tablets, 250 mg, 500 mg, and 750 mg
20-635	047	Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection, 5 mg/mL
21-721	012	Levaquin® (levofloxacin) Oral Solution, 25 mg/mL

We acknowledge receipt of your submissions dated April 19, 2007.

Your submission of January 31, 2007 constituted a complete response to our request letter dated October 30, 2006 and to our subsequent correspondence dated January 21, 2007.

These "Special Supplement - Changes Being Effected" supplemental new drug applications provide for revisions to the package insert and patient package insert for Levaquin® to ensure consistency in the communication of the risks of *Clostridium difficile* associated disease with the use of antimicrobial products, including levofloxacin.

The following revisions (~~strikethrough~~ = deleted and double-underlined = added) to the text for the package insert and patient package insert for Levaquin were proposed in these supplemental applications:

1. The **WARNINGS/Pseudomembranous colitis** subsection (the seventh, eighth, and ninth paragraphs of the **WARNINGS** section) should be replaced with the double underlined text below.

   ~~**Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.**~~

   ~~Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."~~

   ~~After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.~~

   Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including LEVAQUIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

   C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

   If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

2. Under the **PRECAUTIONS/Information for Patients** subsection, please add the following text after the last bullet:

   - that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

3. The **Patient Package Insert/What are the possible side effects of LEVAQUIN?** subsection was modified to add the following text immediately prior to the sentence that begins "If you notice any side effects not mentioned in this leaflet…":

   Diarrhea that usually ends after treatment is a common problem caused by antibiotics. A more serious form of diarrhea can occur during or up to 2 months after use of antibiotics. This has been reported with all antibiotics including with LEVAQUIN. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your physician as soon as possible.

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 text for the package insert and patient package insert.

Within 21 days of the date of this letter, submit 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 in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**SPL for approved supplements NDA 20-634/S-044, NDA 20-635/S-047, NDA 21-721/S-012**."

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

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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