DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634/S-041
NDA 20-635/S-044
NDA 21-721/S-009

SUPPLEMENTAL NDA APPROVAL

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
ATTN: Ms. Alysia Baldwin-Ferro
Director, Regulatory Affairs
920 U.S. Highway 202
Raritan, New Jersey 08869

Dear Ms. Baldwin-Ferro:

Please refer to your November 15, 2006 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Product	Submission Date	Receipt Date
20-634	041	Levaquin® (levofloxacin) Tablets, 250 mg, 500 mg, and 750 mg	November 15, 2006	November 15, 2006
20-635	044	Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection, 5 mg/mL	November 15, 2006	November 15, 2006
21-721	009	Levaquin® (levofloxacin) Oral Solution, 25 mg/mL	November 15, 2006	November 15, 2006

We acknowledge receipt of your submissions dated January 24, 2007, May 15, 2007, August 2, 2007, August 23, 2007, September 13, 2007, and September 14, 2007.

These supplemental new drug applications provide for the treatment of complicated urinary tract infection and acute pyelonephritis with Levaquin 750 mg once daily for five days.

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.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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

1. The **HIGHLIGHTS/ADVERSE REACTIONS** section was modified as follows:

   The most common reactions (≥3%) were nausea, headache, diarrhea, insomnia, ~~and~~ constipation and dizziness (6.2).

2. The table in the **HIGHLIGHTS/DOSAGE AND ADMINITRATION** section has been modified as follows:

   - Dosage in patients with normal renal function (2.1)

Type of Infection	**Dose Every 24 hours**	**Duration (days)**
Nosocomial Pneumonia (1.1)	750 mg	7-14
Community Acquired Pneumonia (1.2)	500 mg	7-14
Community Acquired Pneumonia (1.3)	750 mg	5
Acute Bacterial Sinusitis (1.4)	750 mg	5
	500 mg	10-14
Acute Bacterial Exacerbation of Chronic Bronchitis (1.5)	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI) (1.6)	750 mg	7-14
Uncomplicated SSSI (1.7)	500 mg	7-10
Chronic Bacterial Prostatitis (1.8)	500 mg	28
Complicated Urinary Tract Infection (1.9) or Acute Pyelonephritis (1.11)	750 mg	5
Complicated Urinary Tract Infection (~~1.9~~1.10) or Acute Pyelonephritis (~~1.10~~1.11)	250 mg	10
Uncomplicated Urinary Tract Infection (1.12)	250 mg	3
Inhalational Anthrax (Post-Exposure) (1.13)	500 mg	60

   - Adjust dose for creatinine clearance < 50 mL/min (2.2, 8.6, 12.3)
   - IV Injection, Single-Use or Premix: Slow IV infusion only, over 60 or 90 minutes depending on dose. Avoid rapid or bolus IV (2.4)
   - Dilute single-use vials to 5 mg/mL prior to IV infusion (2.5)
   - Do not mix with other medications in vial or IV line (2.5)

3. The **FULL PRESCRIBING INFORMATION/INDICATIONS AND USAGE** section has been updated with the following information:

1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis [see Clinical Studies (14.7)].*

1.10~~9~~ Complicated Urinary Tract Infections: 10-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa [see Clinical Studies (14.8)]*.

1.11~~10~~ Acute Pyelonephritis; 5 or 10-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of acute pyelonephritis ~~(mild to moderate)~~ caused by *Escherichia coli*, including cases with concurrent bacteremia *[see Clinical Studies (14.7, 14.8)]*.

4. Table 1 in the **FULL PRESCRIBING INFORMATION/2. DOSAGE AND ADMINISTRATION/2.1 Dosage in Patients with Normal Renal Function** section has been modified as follows:

Table 1: Dosage in Patients with Normal Renal Function (creatinine clearance ≥ 50mL/min)

Type of Infection[1]	**Dosed Every 24 hours**	**Duration (days)**[2]
Nosocomial Pneumonia	750 mg	7-14
Community Acquired Pneumonia[3]	500 mg	7-14
Community Acquired Pneumonia[4]	750 mg	5
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10-14
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7-14
Uncomplicated SSSI	500 mg	7-10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[5]	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[6]	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Inhalational Anthrax (Post-Exposure), adult[~~5,6~~7,~~8~~]	500 mg	60[~~5~~8]

[1] Due to the designated pathogens *[see Indications and Usage (1)]*.
[2] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.
[3] Due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae [see Indications and Usage (1.2)]*.
[4] Due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Indications and Usage (1.3)]*.
[5] This regimen is indicated for cUTI due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and AP due to *E. coli*, including cases with concurrent bacteremia.
[6] This regimen is indicated for cUTI due to *Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*; and for AP due to *E. coli.*
[~~5~~7] Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit *[see Clinical Studies (14.9)]*.
[~~6~~8] The safety of LEVAQUIN® in adults for durations of therapy beyond 28 days has not been studied. Prolonged LEVAQUIN® therapy in adults should only be used when the benefit outweighs the risk.

5. The text of the **FULL PRESCRIBING INFORMATION/6. ADVERSE REACTIONS/6.2 Clinical Trial Experience** has been updated with new information as follows (Table 5 and Table 6 has been updated to reflect N = 7537 cases):

   Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

   The data described below reflect exposure to LEVAQUIN® in ~~6994~~7537 patients in ~~28~~29 pooled Phase 3 clinical trials. The population studied had a mean age of ~~49~~50 years (approximately ~~75~~74% of the population was < 65 years of age), ~~51~~50% were male, 71% were Caucasian, 19% were Black. Patients were treated with LEVAQUIN® for a wide variety of infectious diseases *[see Indications and Usage (1)]*. Patients received LEVAQUIN® doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3-14 days, and the mean number of days on therapy was 10 days.

   The overall incidence, type and distribution of adverse reactions was similar in patients receiving LEVAQUIN® doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of LEVAQUIN® due to adverse drug reactions occurred in 4.~~1~~3% of patients overall, 3.8% of patients treated with the 250 mg and 500 mg doses and 5.4% of patients treated with the 750 mg dose. ~~and t~~The most common adverse drug reactions leading to discontinuation ~~was~~with the 250 and 500 mg doses were gastrointestinal (1.4%), primarily nausea (0.6%); vomiting (0.4%); dizziness (0.3%); and headache (0.2%). The most common adverse drug reactions leading to discontinuation with the 750 mg dose were gastrointestinal (1.2%), primarily nausea (0.6%), vomiting (0.5%); dizziness (0.3%); and headache (0.3%).

   Adverse reactions occurring in ≥1% of LEVAQUIN®-treated patients and less common adverse reactions, occurring in 0.1 to <1% of LEVAQUIN®-treated patients, are shown in Table 5 and Table 6, respectively. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, ~~and~~ constipation, and dizziness.

6. The following sections have been added to the **FULL PRESCRIBING INFORMATION/14. CLINICAL STUDIES** section:

   14.7 Complicated Urinary Tract Infections and Acute Pyelonephritis: 5-day Treatment Regimen

   To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 1109 patients with cUTI and AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from November 2004 to April 2006 comparing LEVAQUIN® 750 mg i.v. or orally once daily for 5 days (546 patients) with ciprofloxacin

400 mg i.v. or 500 mg orally twice daily for 10 days (563 patients). Patients with AP complicated by underlying renal diseases or conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital malformation were excluded. Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a pathogen identified at baseline. The post-therapy (test-of-cure) visit occurred 10 to 14 days after the last active dose of LEVAQUIN® and 5 to 9 days after the last dose of active ciprofloxacin.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 19.

Table 19: Bacteriologic Eradication at Test-of-Cure

	LEVAQUIN® 750 mg orally or IV once daily for 5 days		**Ciprofloxacin** 400 mg IV/500 mg orally twice daily for 10 days		**Overall Difference [95% CI]**
	n/N	%	n/N	%	LEVAQUIN®-Ciprofloxacin
mITT Population[a]					
Overall (cUTI or AP)	252/333	75.7	239/318	75.2	0.5 (-6.1, 7.1)
cUTI	168/230	73.0	157/213	73.7	
AP	84/103	81.6	82/105	78.1	
Microbiologically Evaluable Population[b]					
Overall (cUTI or AP)	228/265	86.0	215/241	89.2	-3.2 [-8.9, 2.5]
cUTI	154/185	83.2	144/165	87.3	
AP	74/80	92.5	71/76	93.4	

[a] The mITT population included patients who received study medication and who had a positive ($\geq 10^5$ CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.

[b] The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at $> 10^5$ CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to follow-up, and compliance with treatment (among other criteria).

Microbiologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to LEVAQUIN® treatment are presented in Table 20.

Table 20: Microbiological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to LEVAQUIN® 750 mg QD for 5 Days Treatment

Pathogen	**Microbiologic Eradication Rate (n/N)**	**%**
*Escherichia coli**	155/172	90
Klebsiella pneumoniae	20/23	87
Proteus mirabilis	12/12	100

* The predominant organism isolated from patients with AP was *E. coli*: 91% (63/69) eradication in AP and 89% (92/103) in patients with cUTI.

14.8 Complicated Urinary Tract Infections and Acute Pyelonephritis: 10-day Treatment Regimen

To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen of LEVAQUIN®, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from June 1993 to January 1995 comparing LEVAQUIN® 250 orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol amendment which took place after 30% of enrollment. Microbiological efficacy was measured by bacteriologic eradication of the baseline organism(s) at 1-12 days post-therapy in patients with a pathogen identified at baseline.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in **Table** Table 21.

Table 21. Bacteriologic Eradication Overall (cUTI or AP) at Test-Of-Cure[a]

	LEVAQUIN® 250 mg once daily for 10 days		**Ciprofloxacin** 500 mg twice daily for 10 days	
	n/N	%	n/N	%
mITT Population[b]	174/209	83.3	184/219	84.0
Microbiologically Evaluable Population[c]	164/177	92.7	159/171	93.0

[a] 1-9 days posttherapy for 30% of subjects enrolled prior to a protocol amendment; 5-12 days posttherapy for 70% of subjects.
[b] The mITT population included patients who had a pathogen isolated at baseline. Patients with missing response were counted as failures in this analysis.
[c] The Microbiologically Evaluable population included mITT patients who met protocol-specified evaluability criteria.

7. The **FULL PRESCRIBING INFORMATION/17. PATIENT COUNSELING INFORMATION/17.5 FDA-Approved Patient Labeling/What are the possible side effects of LEVAQUIN?** subsection was updated as follows:

   LEVAQUIN® is generally well tolerated. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, ~~and~~ constipation, and dizziness.

8. Minor editing corrections throughout the labeling.

CONTENT OF LABELING

As soon as possible, but no later than one month from the date of this letter, 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-041, NDA 20-635/S-044, and NDA 21-721/S-009**."

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for these applications.

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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