DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634/S-040
NDA 20-635/S-043
NDA 21-721/S-007

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Ms. Cynthia Chianese
Director, Regulatory Affairs
1000 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Chianese:

Please refer to your supplemental drug applications, dated December 29, 2005 and received on December 30, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Product
20-634	040	Levaquin® (levofloxacin) Tablets, 250 mg, 500 mg, and 750 mg
20-635	043	Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection
21-721	007	Levaquin® (levofloxacin) Oral Solution, 25 mg/mL

We acknowledge receipt of your submissions dated June 12, 2006.

These supplemental applications provide for the following revisions to the text for the package insert (~~strikethrough~~ = deleted and <u>double-underlined</u> = added):

1. The **CLINICAL PHARMACOLOGY/MICROBIOLOGY/Susceptibility Tests/Dilution techniques** subsection of the package insert was revised as follows:

   Dilution techniques:

   Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* ~~Enterococci~~*Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, and *Pseudomonas aeruginosa:*

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[a]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* ~~spp. including *S.*~~ *pneumoniae*[b] and *S. pyogenes*:

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

2. The **CLINICAL PHARMACOLOGY/MICROBIOLOGY/Susceptibility Tests/Diffusion techniques** subsection of the package insert was revised as follows:

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg levofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, ~~Enterococci~~*Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, and *Pseudomonas aeruginosa*:

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[e]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* ~~spp. including *S.*~~ *pneumoniae*[f] and *S. pyogenes*:

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus* spp. including *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

3. The **INDICATIONS AND USAGE** section of the package insert was revised as follows**:**

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae, or Moraxella catarrhalis.*

Acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis*.

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,* or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended. (See **CLINICAL STUDIES.)**

Community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant strains [MDRSP])*, *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES.**)

* MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2µg/ml), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes,* or *Proteus mirabilis*.

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes*.

Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or methicillin-susceptible *Staphylococcus epidermidis*.

Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa*.

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli*.

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus*.

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized ~~prevent the development of inhalational anthrax following exposure to~~ *Bacillus anthracis.* (See **DOSAGE AND ADMINISTRATION** and **ADDITIONAL INFORMATION - INHALATIONAL ANTHRAX**).

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 to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15

of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions **"FPL for approved supplement NDA 20-634/S-040, NDA 20-635/S-043, and NDA 21-721/S-007."** Approval of these submissions by FDA is not required before the labeling is used.

The electronic labeling rule published December 11, 2003 (FR 69009) requires submission of content of labeling [21 CFR 201.100(d)(3)] in electronic format effective June 8, 2004. For additional information, consult the guidance for industry *Providing Regulatory Submissions in Electronic Format - Content of Labeling* (April 2005). The guidance specifies that, as of fall 2005, content of labeling is to be submitted in structured product labeling (SPL) format. To facilitate our review of your submission, we ask that labeling also be submitted in MS Word format with proposed revisions clearly indicated.

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 these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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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