



NDA 20-634/S-047
NDA 20-635/S-051
NDA 21-721/S-015

SUPPLEMENTAL NDA APPROVAL

Ortho-McNeil-Janssen Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
ATTN: Ms. Ilona Scott
Director, Global Regulatory Affairs
920 U.S. Highway 202 South
P.O. Box 300
Raritan, New Jersey 08869

Dear Ms. Scott:

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 Number	Supplement Number	Drug Product	Submission Date	Receipt Date
20-634	047	LEVAQUIN [®] (levofloxacin) Tablets, 250 mg, 500 mg, and 750 mg	July 3, 2007	July 5, 2007
20-635	051	LEVAQUIN [®] (levofloxacin) Injection and Levaquin [®] (levofloxacin in 5% dextrose) Injection, 5 mg/mL	July 3, 2007	July 5, 2007
21-721	015	LEVAQUIN [®] (levofloxacin) Oral Solution, 25 mg/mL	July 3, 2007	July 5, 2007

We acknowledge receipt of your submissions dated December 20, 2007, May 1, 2008, and May 5, 2008 (2).

These supplemental new drug applications provide for the use of LEVAQUIN[®] for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis* in pediatric patients (≥ 6 month of age and older).

We have completed our review of these supplemental applications, as amended. According to the regulations for accelerated approval, we have concluded that adequate information has been presented to approve LEVAQUIN[®] for use as recommended in the agreed-upon labeling text (enclosed). Accordingly, these applications are approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of these drug products and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The revisions to the content of labeling for the package insert for these supplemental NDAs for LEVAQUIN[®] are as follows (~~struck through~~ = deleted and double-underlined = added):

1. The **HIGHLIGHTS/DOSAGE AND ADMINISTRATION** subsection was revised 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 (1.10) or Acute Pyelonephritis (1.11)	250 mg	10
Uncomplicated Urinary Tract Infection (1.12)	250 mg	3
Inhalational Anthrax (Post-Exposure) (1.13) Adults <u>and Pediatric Patients > 50 kg</u> <u>Pediatric Patients < 50 kg</u>	500 mg <u>8 mg/kg BID</u> <u>(not to exceed 250 mg per dose)</u>	60 <u>60</u>

- Adjust dose for creatinine clearance < 50 mL/min (2.3, 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 (2.5)
- Dilute single-use vials to 5 mg/mL prior to IV infusion (2.6)
- Do not mix with other medications in vial or IV line (2.6)

2. The fourth bullet of the **HIGHLIGHTS/WARNINGS AND PRECAUTIONS** subsection of the package insert was revised as follows:

- Achilles or other tendon rupture, risk is increased with concomitant corticosteroids; especially the elderly and in patients over 65 years of age. Discontinue if pain or inflammation in a tendon occurs (5.3, 8.5)

3. The **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS/Pediatrics** subsection was revised as follows:

Pediatrics: Musculoskeletal disorders (arthralgia, arthritis, tendonopathy, and gait abnormality) seen in more LEVAQUIN[®]-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.8, 8.4, 13.2). Safety in pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (post-exposure) (1.13, 2.2, 8.4, 14.9).

4. The **FULL PRESCRIBING INFORMATION/1. INDICATIONS AND USAGE/1.13 Inhalational Anthrax (Post-Exposure)** subsection was revised as follows:

1.13 Inhalational Anthrax (Post-Exposure)

LEVAQUIN[®] is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. The effectiveness of LEVAQUIN[®] is based on plasma concentrations achieved in humans, a surrogate ~~marker~~ considered endpoint reasonably likely to predict efficacy/clinical benefit. LEVAQUIN[®] has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of LEVAQUIN[®] in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged LEVAQUIN[®] therapy ~~in adults~~ should only be used when the benefit outweighs the risk [see *Dosage and Administration (2.1, 2.2)* and *Clinical Studies (14.9)*].

5. The **Table 1. Dosage in Adult Patients with Normal Renal Function (creatinine clearance ≥ 50mL/min)** in the **FULL PRESCRIBING INFORMATION/2. DOSAGE AND ADMINISTRATION/ 2.1 Dosage in Adult Patients with Normal Renal Function** subsection was revised as follows:

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 <u>and pediatric patients >50 kg</u> ^{7,8}	500 mg	60 ⁸
<u>Pediatric patients < 50 kg</u> ^{7,8}	See table below (2.2)	60 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*.
- 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)].
- ⁸ The safety of LEVAQUIN[®] in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients (See Warnings and Precautions (5.7), Use in Specific Populations (8.4), and Clinical Studies [14.9]). Prolonged LEVAQUIN[®] therapy ~~in adults~~ should only be used when the benefit outweighs the risk.

6. The **FULL PRESCRIBING INFORMATION/2. DOSAGE AND ADMINISTRATION/2.2 Dosage in Pediatric Patients** subsection was added as follows:

2.2 Dosage in Pediatric Patients

<u>Type of Infection¹</u>	<u>Dose</u>	<u>Freq. Once every</u>	<u>Duration²</u>
<u>Inhalational Anthrax (post-exposure)^{3, 4}</u>			
<u>Pediatric patients > 50 kg</u>	<u>500 mg</u>	<u>24hr</u>	<u>60 days⁴</u>
<u>Pediatric patients < 50 kg</u>	<u>8 mg/kg</u> <u>(not to exceed</u> <u>250 mg per dose)</u>	<u>12hr</u>	<u>60 days⁴</u>

¹ Due to *Bacillus anthracis* (See Indications and Usage [1.13].)

² Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

³ 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])

⁴ The safety of LEVAQUIN[®] in pediatric patients for durations of therapy beyond 14 has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients (See *Warnings and Precautions* (5.7), *Use in Specific Populations* (8.4), and *Clinical Studies* [14.9]) Prolonged LEVAQUIN[®] therapy should only be used when the benefit outweighs the risk.

7. The title, **FULL PRESCRIBING INFORMATION/2. DOSAGE AND ADMINISTRATION/ 2.2.3 Dosage Adjustment in Adults Patients with Renal Impairment**, was revised.

8. The **FULL PRESCRIBING INFORMATION/5. WARNINGS AND PRECAUTIONS/5.4 Tendon Effects** subsection was revised as follows:

5.4 Tendon Effects

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 LEVAQUIN[®]. Postmarketing surveillance reports indicate that this risk is increased in patients receiving concomitant corticosteroids, especially the elderly and in patients over 65 years of age. LEVAQUIN[®] should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can

occur during or after therapy with quinolones, including LEVAQUIN® [see Adverse Reactions (6); Patient Counseling Information (17.3)].

9. The **FULL PRESCRIBING INFORMATION/5. WARNINGS AND PRECAUTIONS/5.9 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals** subsection was revised as follows:

5.9 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

LEVAQUIN® is ~~not~~ indicated ~~for~~ in pediatric patients (less than 18 years of age) only for the prevention of inhalational anthrax (post-exposure) [see Indications and Usage (1.13)]. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendonopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving LEVAQUIN® [see Use in Specific Populations (8.4)].

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species [see *Nonclinical Toxicology Animal Toxicology and/or Pharmacology* (13.2)].

10. The **FULL PRESCRIBING INFORMATION/8. USE IN SPECIFIC POPULATIONS/8.4 Pediatric Use** subsection was revised as follows:

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. [See *Warnings and Precautions* (5.7) and Animal Toxicology and/or Pharmacology [13.2]]

~~LEVAQUIN® is not indicated for pediatric patients (less than 18 years of age) (See Warnings and Precautions [5.8]).~~

Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been studied. The pharmacokinetics of levofloxacin following a single intravenous dose were investigated in pediatric patients ranging in age from six months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients resulting in lower plasma exposures than adults for a given mg/kg dose. (See Indications and Usage [1.13], Dosage and Administration [2.2], Clinical Pharmacology [12.3] and Clinical Studies [14.9]).

Adverse Events

In clinical trials, 1534 children (6 months to 16 years of age) were treated with oral and intravenous LEVAQUIN[®]. Children 6 months to 5 years of age received LEVAQUIN[®] 10 mg/kg twice a day and children greater than 5 years of age received 10 mg/kg once a day (maximum 500 mg per day) for approximately 10 days.

A subset of children in the clinical trials (1340 LEVAQUIN[®]-treated and 893 non-fluoroquinolone-treated) enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendonopathy, gait abnormality) during 60 days and 1 year following the first dose of study drug. Children treated with LEVAQUIN[®] had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children as illustrated in Table 1.

Table 1: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

Follow-up Period	LEVAQUIN [®] N = 1340	Non-Fluoroquinolone ^a N = 893	p-value ^b
60 days	28 (2.1%)	8 (0.9%)	p = 0.038
1 year ^c	46 (3.4%)	16 (1.8%)	p = 0.025

^a Non-Fluoroquinolone: ceftriaxone, amoxicillin/ clavulanate, clarithromycin

^b 2-sided Fisher's Exact Test

^c There were 1199 LEVAQUIN[®]-treated and 804 non-fluoroquinolone-treated children who had a one-year evaluation visit. However, the incidence of musculoskeletal disorders were calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

Arthralgia was the most frequently occurring musculoskeletal disorder in both treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%) LEVAQUIN[®]-treated children and most were treated with analgesics. The median time to resolution was 7 days for LEVAQUIN[®]-treated children and 9 for non-fluoroquinolone-treated children (approximately 80% resolved within 2 months in both groups). No child had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae.

Vomiting and diarrhea were the most frequently reported adverse events, occurring in similar frequency in the LEVAQUIN[®]-treated and non-fluoroquinolone-treated children.

In addition to the events reported in pediatric patients in clinical trials, events reported in adults during clinical trials or post-marketing experience may also be expected to occur in pediatric patients.

11. A paragraph containing pediatric information was added to the **FULL PRESCRIBING INFORMATION/12. CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics** subsection as follows:

Pediatrics

The pharmacokinetics of levofloxacin following a single 7 mg/kg intravenous dose were investigated in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients, resulting in lower plasma exposures than adults for a given mg/kg dose. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 8.0 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures (AUC_{0-24} and C_{max}) to those observed in adult patients administered 500 mg of levofloxacin once every 24 hours.

12. The **FULL PRESCRIBING INFORMATION/14. CLINICAL STUDIES/14.9 Inhalational Anthrax (Post-Exposure)** subsection was revised as follows:

The effectiveness of LEVAQUIN[®] for this indication is based on plasma concentrations achieved in humans, a surrogate ~~marker~~ endpoint reasonably likely to predict efficacy/clinical benefit. LEVAQUIN[®] has not been tested in humans for the post-exposure prevention of inhalation anthrax. The mean plasma concentrations of LEVAQUIN[®] associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens [*see Indications and Usage (1.13); Dosage and Administration (2.1, 2.2)*].

~~Levofloxacin pharmacokinetics were evaluated in various populations. Levofloxacin plasma concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication. The mean (\pm s.d.) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.1 ± 0.8 and 6.2 ± 1.0 mcg/mL, respectively; and the corresponding total exposure is 47.9 ± 6.8 and 48.3 ± 5.4 mcg-h/mL, respectively. Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (\pm SD) steady-state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0-24}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg-h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily [*see Clinical Pharmacology (12.3)*].~~

In adults, the safety of LEVAQUIN[®] for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at 500 mg daily up to 60 days is limited. Prolonged LEVAQUIN[®] therapy in adults should only be used when the benefit outweighs the risk.

In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of musculoskeletal adverse events (arthralgia, arthritis, tendonopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited. [See Warnings and Precautions (5.7), Use in Specific Populations (8.4)].

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD₅₀ (~2.7 X 10⁶) spores (range 17 - 118 LD₅₀) of *B. anthracis* (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 mcg/mL. ~~Mean-s~~Steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL. Mean (SD) steady state AUC₀₋₂₄ was 33.3 + 3.2 mcg·hr/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral LEVAQUIN[®] beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [P=0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

13. Another bullet for musculoskeletal disorders in pediatric patients 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:

- **Musculoskeletal Disorders in Pediatric Patients:** Parents should inform their child's physician if their child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any tendon or joint-related problems that occur during or following LEVAQUIN[®] therapy (See Warnings and Precautions [5.7] and Use in Specific Populations [8.4]).

14. The **FULL PRESCRIBING INFORMATION/17. PATIENT COUNSELING INFORMATION/17.5 FDA-Approved Patient Labeling/Patient Information About Levaquin/Who should not take Levaquin?** subsection was revised as follows:

You should not take LEVAQUIN[®] if you have ever had a severe allergic reaction to any of the group of antibiotics known as “quinolones” such as ciprofloxacin. Serious and occasionally fatal allergic reactions have been reported in patients receiving therapy with quinolones, including LEVAQUIN[®].

If you are pregnant or are planning to become pregnant while taking LEVAQUIN[®], talk to your health care professional before taking this medication. LEVAQUIN[®] is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

~~LEVAQUIN[®] is not recommended for children. Due to possible side effects, LEVAQUIN[®] is not recommended for pediatric patients except in the prevention of anthrax after inhalational exposure.~~

15. The following information was added to the **FULL PRESCRIBING INFORMATION/17. PATIENT COUNSELING INFORMATION/17.5 FDA-Approved Patient Labeling/Patient Information About Levaquin** subsection:

What if I have been prescribed LEVAQUIN[®] for possible anthrax exposure?

LEVAQUIN[®] has been approved to reduce the chance of developing anthrax infection following exposure to the anthrax bacteria. With the exception of using LEVAQUIN[®] to prevent anthrax after possible exposure, LEVAQUIN[®] is not recommended for children. If you are pregnant, or plan to become pregnant while taking LEVAQUIN[®], you and your doctor should discuss if the benefits of taking LEVAQUIN[®] for anthrax outweigh the risks.

LEVAQUIN[®] is generally well tolerated. Side effects that may occur during treatment to prevent anthrax might be acceptable due to the seriousness of the disease. You and your doctor should discuss the risks of not taking your medicine against the risks of experiencing side effects.

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

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(1)] 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-047, NDA 20-635/S-051, and NDA 21-721/S-015.**”

POSTMARKETING COMMITMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing study commitment (Subpart H Postmarketing Study Commitment) specified in your submissions dated May 5, 2008. This commitment is listed below:

1. To cooperate with U.S.-based public health agencies in evaluating data on the use of LEVAQUIN (levofloxacin) in a large U.S population for inhalational anthrax (post exposure) prophylaxis, should an exposure occur. This includes long-term safety data in pediatric patients from treatment greater than 14 days, if such data become available.

Final study reports should be submitted to these NDAs as supplemental applications. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated “**Subpart H Postmarketing Study Commitments.**”

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).

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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

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/s/

Renata Albrecht
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