

Division Director Review

APPLICANT: Johnson & Johnson

NDA/DRUG: NDA 20-634/S-047 levofloxacin tablets
NDA 20-635/S-051 levofloxacin injection
NDA 21-721/S-015 levofloxacin oral solution

TRADE NAME: Levaquin

Date of Submission: July 3, 2007

PDUFA Goal Date: May 5, 2008

Indication: Inhalational Anthrax (post-exposure) To prevent or reduce incidence of disease after exposure to the spores of *Bacillus anthracis*

Related Material: **Material Reviewed:**
Clinical: Joette Meyer
Clinical Pharmacology: Seong Jang, Phil Colangelo
Pharmacometrics: Fang Li, Christoffer Tornoe
Administrative Action Package

RECOMMENDATIONS:

The applicant should be issued an approval letter for the use of levaquin for pediatric patients to prevent anthrax. The INDICATION AND USAGE section has been revised (new text underlined) and a **Dosage in Pediatric Patients** subsection has been added in DOSAGE AND ADMINISTRATION sections as shown below:

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 endpoint reasonably likely to predict 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 should only be used when the benefit outweighs the risk [*see Dosage and Administration (2.1, 2.2) and Clinical Studies (14.9)*].

2.1 Dosage in Adult Patients with Normal Renal Function

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

Type of Infection ¹	Dosed Every 24 hours	Duration (days) ²
Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg ^{7,8}	500 mg	60 ⁸
Pediatric patients < 50 kg ^{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 (5.9)*, *Use in Specific Populations (8.4)*, and *Clinical Studies (14.9)*] Prolonged LEVAQUIN[®] therapy should only be used when the benefit outweighs the risk.

2.2 Dosage in Pediatric Patients

Type of Infection ¹	Dose	Freq. Once every	Duration ²
Inhalational Anthrax (post-exposure) ^{3,4}			
Pediatric patients > 50 kg	500 mg	24hr	60 days
Pediatric patients < 50 kg	8 mg/kg (not to exceed 250 mg per dose)	12hr	60 days ⁴

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 (5.8)*, *Use in Specific Populations (8.40)*, and [Clinical Studies \[14.9\]](#)) Prolonged LEVAQUIN[®] therapy should only be used when the benefit outweighs the risk.

INTRODUCTION:

As summarized in the Clinical Review, these supplements to extend the post-exposure prophylaxis indication of levaquin to pediatric patients were submitted on July 3, 2007. J&J originally requested approval of levofloxacin for use in the pediatric population as part of the supplements requesting adult approval; these were submitted May 25, 2004. The indication was approved in adults under Subpart H (surrogate endpoint) on November 24, 2004 (NDA 20-634/S-035, NDA 20-635/S-035, NDA 21-721/S-003). However, there was no information on the safety of levofloxacin in pediatric patients, therefore the applicant chose to withdraw the pediatric supplements in November 2004 (these were administratively split from the adult supplements).

Subsequently, Johnson & Johnson evaluated the safety and efficacy of levofloxacin in pediatric patients under a pediatric written request issued June 16, 2006 and evaluated 1340 levofloxacin and 893 non-fluoroquinolone control pediatric patients ranging in age from 6 months to 16 years. These patients were treated with levofloxacin 10 mg/kg QD (patients older than 5 years) or 10 mg/kg BID (patients younger than 5 years) for durations up to 14 days. The clinical studies and safety data were submitted to the FDA December 20, 2006, reviewed, and included in labeling approved for these supplements (NDA 20-634/S-043, NDA 20-635/S-046, NDA 21-721/S-011) on September 11, 2007. It was noted that levofloxacin treated patients had a significantly higher rate of musculoskeletal adverse events compared to patients treated with other antibacterials. 2.1% vs 0.9%, $p=0.038$ at the end of a 60 day follow up (off treatment). The events were mostly arthralgia in weight bearing joints, most were judged mild and resolved. The most common adverse events in pediatric patients were nausea and vomiting.

After review of their PK and clinical studies, Johnson & Johnson proposed to use the 10 mg/kg BID or QD regimens they tested in the CAP study conducted in response to the pediatric written request and recommend these for pediatric patients in post-exposure prophylaxis of inhalational anthrax.

BACKGROUND:

Anthrax is a bacterial infection caused by *Bacillus anthracis*. It virtually does not occur naturally in the 21st century, and only about 100 naturally-occurring cases were reported in the US in the 20th century. However, the organism is a CDC Category A agent considered likely to be used in a bioterrorism attack, therefore drugs for the prevention or treatment of the infection are needed.¹

In August 2000, FDA approved ciprofloxacin for the post-exposure prophylaxis on anthrax in both adult and pediatric patients. This was done after comprehensive review of the ciprofloxacin safety profile, including data on the use of ciprofloxacin for up to 60 days, review of a rhesus monkey study of post-exposure inhalational anthrax in which ciprofloxacin treated animals had a statistically significant survival rate compared to placebo treated animals², and comparison demonstrating that plasma concentrations (exposures) to levofloxacin in humans were at least as high as concentrations achieved in surviving animals. Ciprofloxacin was already an approved antimicrobial, effective in a range of infectious diseases. Therefore, the applications were approved under Subpart H, using the concentrations/exposure as the surrogate endpoint likely to predict the clinical endpoint. During the events of 2001, CDC gathered data on patients who received ciprofloxacin post-exposure prophylaxis, enabling Bayer to submit the information on approximately 9300 persons, fulfilling the postmarketing commitment to provide data in the event of anthrax dissemination.

Penicillin G and tetracycline drugs (tetracycline, doxycycline, minocycline) have anthrax among their labeled indications. The labeling for these products was updated based on the Federal Register notice published in 2001³ to include information on doses to use in post exposure prophylaxis.

¹ Inglesby, T et al. The Working Group for Civilian Biodefence. Anthrax as a biologic weapon, 2002. JAMA 2002;287:2236-2252.

² Friedlander AM et al. Postexposure prophylaxis against experimental inhalation anthrax. J Infect Dis. 1993 May;167(5):1239-43.

³ Federal Register: November 2, 2001 (Volume 66, Number 213, Page 55679-55682) [Docket No. 01N-0494] Prescription Drug Products; Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure)

Although there are three products approved for this indication, including one fluoroquinolone, alternative therapy is useful in situations where (a) access to drugs is limited, as happened during 2001, (b) patients do not tolerate a product, or (c) safety data for 60 day duration is not available, and shorter durations of one product may be used.

In these applications, data on patients who received 7 mg/kg in pediatric pharmacokinetic studies and 10 mg/kg QD or BID in treatment studies was evaluated. Pharmacokinetic modeling was conducted and showed that the dose that provides a good match to the adult exposure in pediatric patients is 8 mg/kg (max 250 mg) per dose, given BID. While this dose is higher than the dose studied in the PK studies, it is below the 10 mg/kg doses studied in clinical studies of over 1500 pediatric patients. While the model was developed and tested for a regimen of 7.5 mg/kg bid, the dose was adjusted to 8 mg/kg because (a) the C_{max}, C_{min} and AUC of the 7.5 and 8 mg/kg doses were within 10% of each other and within the adult 500 mg and 750 mg QD dose, and (b) the 8 mg/kg would more likely minimize medication errors by omitting a decimal point as part of the dose.

REVIEW OF THE APPLICATIONS:

Based on the safety data provided for levofloxacin in pediatric patients, the drug is an alternative to currently approved treatments; it does not appear to offer any advantages over the existing treatments based on the data submitted. Specifically, musculoskeletal adverse events are higher in the levofloxacin arm, as in the ciprofloxacin arm, compared to cephalosporins; however, no cephalosporin is approved for treating anthrax. While penicillin G and doxycycline do not cause such musculoskeletal reactions, they cause allergic, hematologic, or other adverse reactions

Levofloxacin is rapidly and well absorbed – 99% of oral dose is absorbed. It has linear pharmacokinetics and reaches steady state conditions by 48 hours in adults. It is widely distributed in body tissues, and is not metabolized and it is cleared primarily through urine. Half life in adults is 6-8 hours.

The Clinical Pharmacology and Pharmacometrics team reviewed the applications and their review provides details on the approach, the information and rationale for the 7.5 mg/kg BID regimen modeled and the 8 mg/kg BID regimen recommended for approval. In summary, they used data from three pediatric PK studies (total 90 male and female subjects) and two adult PK studies (47 subject), developed a model, showed that the 7.5 mg/kg dosage regimen best approximated the AUC of the adult 500 mg dose. The Phase 3 population PK data was considered insufficient to include in the model. Subsequently, the pharmacometrics reviewers showed that the model could be used to predict concentrations following 10 mg/kg dosing, and compared these to actual concentrations measured from patients in the Phase 3 studies who received either 10 mg/kg BID (<5 year old) or 10 mg/kg QD (>5 years old). The 10 mg/kg dosing regimen proposed and evaluated in the community-acquired pneumonia (CAP) and acute otitis media studies resulted in approximately 40% overexposure in younger patients compared to adults, and 15% underexposure in older children, compared to adult exposure. The doses were considered effective in the treatment of CAP in these patients, although it was noted that the majority had a serological diagnosis of *Mycoplasma pneumoniae* – the information on the safety and efficacy of the community acquired pneumonia study and the 10 mg/kg regimens is summarized in the review for NDA 20-634/S-043, NDA 20-635/S-046, and NDA 21-721/S-011. The data on the acute otitis media study are also summarized. Subsequently, the reviewers predicted the AUC, C_{max} and C_{min} of the 8 mg/kg dose, which was within 10% of the previously modeled dose and acceptably approximated the adult doses.

Based on this modeling, a dose of 15 mg/kg per day provides AUC that approximates the exposure achieved in adults after 500 mg QD), and exceeds the exposure achieved in the monkey efficacy study; therefore the 16 mg/kg per day total dose is also predicted to be effective. To best approximate C_{max} and troughs, children need to receive the drug at 7.5 mg/kg BIDs given their faster clearance, and this can be rounded up to 8 mg/kg without exceeding the exposures seen in adults given 500 mg and 750 mg QD. Interestingly, the BID regimen is analogous to the regimen tested in monkeys where the monkeys also needed to receive two daily doses because of rapid clearance. In monkeys, however, the goal was never to exceed the adult AUC or the adult concentration over the 24 hour period (adults are dosed 500 mg QD), therefore monkeys received a dose of 15 mg/kg in the morning, followed by a 4 mg/kg dose in the evening. The 7.5 mg/kg BID or 8 mg/kg BID regimen not only approximates the exposures and concentrations achieved in adults, but also exceeds these values compared to those achieved in the monkeys. The exposures and concentrations following the pediatric doses were within the values corresponding to the adult 750 mg QD. The safety of the 10 mg/kg dosing regimens was evaluated in pediatric patients in the CAP study, and therefore, there is sufficient information on safety in pediatric patients. Of note, in addition to the gastrointestinal side effects seen with fluoroquinolones, including levofloxacin, there was a greater incidence of musculoskeletal adverse events reported in the levofloxacin arm.

This regimen is recommended for ages >6 months, and should be given BID for pediatric patients up to 500 mg in age because Cmax in children weighing less than 50 kg would approximate or exceed the Cmax achieved in adults after the 750 mg dose, and there are no safety data in adults or in children for such high Cmax values.

Although pediatric patients did not specifically receive the 8 mg/kg BID regimen being proposed, there are data from three pediatric studies at 7 mg/kg, adult PK data, safety and efficacy data from clinical studies evaluating the higher dose of 10 mg/kg BID or QD in pediatric patients, and the extrapolation from the animal efficacy study regarding exposures that yielded efficacy. Specifically, the levels achieved in animals were lower than the exposures reached with 7 mg/kg, therefore 8 mg/kg would also be effective. The 8 mg/kg most closely matches the pharmacokinetic parameters achieved in adults. Finally, the 10 mg/kg dosage regimens were tested in over 1500 pediatric patients, (1340 had 1 year followup to evaluate musculoskeletal adverse events). These studies show that in addition to the common gastrointestinal adverse reactions of nausea and vomiting (seen also with other antimicrobials), class-related musculoskeletal adverse events were seen in 2.1% levofloxacin vs 0.9% of non-fluoroquinolone treated patients. However, this finding is similar to results in pediatric patients treated with ciprofloxacin in the comparative study vs. a non-fluoroquinolone, and is currently labeled. The number of patients within each stratum by age are reported in the following table:

N	1340	893
<2 years	631 (47))	452 (51)
2-<6 years	516 (39)	379 (42)
6-<12 years	148 (11)	48 (5)
12-<17 years	45 (3)	14 (2)

In summary, because levofloxacin has linear kinetics and highly predictable pharmacokinetic modeling, data from pediatric and adult PK studies could be successfully used to determine the dose in pediatric patients that best approximates the adult 500 mg dose, and also is comparable to or exceeds exposure in the monkey efficacy study. In addition to safety from the 90 patients who received 7 mg/kg in the Phase I PK studies, there are data on over 1500 pediatric patients who received 10 mg/kg doses in Phase 3 otitis media and CAP studies. The duration of treatment was up to 14 days, therefore this duration is reflected in the labeling to be approved.

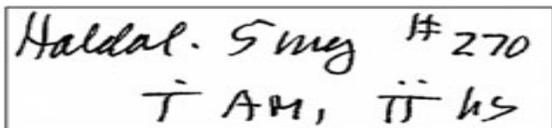
Because no clinical data on 8 mg/kg BID was available, examples of drugs approved for pediatric use on the basis of modeling were examined. Four products approved for use in pediatric patients were identified; these also relied on a composite of information from adult data, pediatric data, and modeling: sotalol for maintenance of normal sinus rhythm, Zosyn for intra-abdominal infections, Trileptal for treatment of partial seizures, and Busulfan for myelogenous leukemia. Therefore, these examples further support approval of the levofloxacin regimen.

JOHNSON & JOHNSON PROPOSAL:

The company agreed with the Division’s pharmacokinetic analyses and dosing recommendations for the 7.5 mg/kg BID regimen; however, they noted that medication errors are likely to happen when doses have decimal points, as cited in publications they provided.⁴ In one of the publications, it was pointed out how a dose of 0.5 mg Haldol was erroneously filled at a 5 mg dose because the leading zero was absent and the decimal point was overlooked.

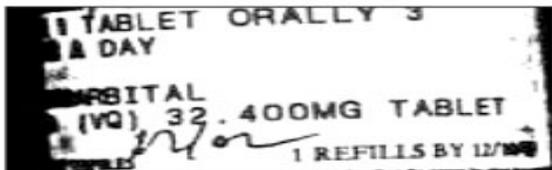
⁴ T. S. Lesar, L. Briceland and D. S. Stein T. S. Factors related to errors in medication prescribing. *JAMA*. 1997;277(4):312-317

Grissinger M and S Roulx, US Pharmacist. Let’s Get to the Point! *US Pharmacist* 2008; 33(1):74.



Haldol. 5mg #270
T AM, T HS

Without a leading zero, this prescription was misinterpreted and dispensed as "Haldol 5 mg."



1 TABLET ORALLY 3
A DAY
HOSPITAL
(VQ) 32.400MG TABLET
1 REFILLS BY 12/10/08

In this computer-generated label, the use of trailing zeros could cause confusion.

The review team considered the proposal and conducted additional predictions of C_{max}, C_{min} and AUC if the recommended dose were rounded off to 8 mg/kg BID up to a max of 250 mg per dose. As shown in the figures below, the 8 mg/kg dose provides pharmacokinetic characteristics that exceed those valued measured in the monkey post-exposure anthrax model and is within the range studied previously in children and adults who received 750 mg QD. Therefore, the pharmacometric team recommended the following in the review dated March 5, 2008:

- ≥ 6 months and ≤ 50 kg: 8 mg/kg b.i.d. (not to exceed 250 mg/dose)
- >50 kg: 500 mg q.d.

Safety data are available for duration of 14 days, therefore the labeling will reflect this information.

DISCIPLINE SPECIFIC COMMENTS:

Clinical: As noted above, J&J has provided safety data in over 1500 pediatric patients, 1340 of whom had 1 year follow up off drug to evaluate musculoskeletal adverse events. The safety data support approval of the pediatric indication from >6 months through 16 years for durations up to 14 days.

On May 5, 2008, J&JPRD agreed to the following Subpart H Postmarketing Study Commitment:

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.

Clinical Pharmacology/Pharmacometrics:

The Pharmacometrics review should be consulted for complete presentation and discussion of the pharmacometric modeling. Although the 8 mg/kg BID dose is based on modeling, no postmarketing Phase 1 study is needed to test this regimen in pediatric volunteers. This question was raised with the Clinical Pharmacology staff who reported that such studies are not requested, noting the precedents cited above for sotalol, Zosyn, Trileptal, and Busulfan, above.

Statistics: There is no new information.

Chemistry: There is no new information.

Microbiology: There is no new information.

Pharmacology /Toxicology: There is no new information.

Labeling:

The labeling submitted May 5, 2008 includes all the changes upon which the Division and company agreed.

RECOMMENDATIONS:

These supplements should be issued an approval letter, under 21 CFR 314.500 Subpart H.

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/s/

Renata Albrecht
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