

CLINICAL REVIEW

Application Type	NDAs 20-634/S-047 (tablets) 20-635/S-051 (injection) 21-721/S-015 (oral solution)
Submission Code	SE-5
Letter Date	July 3, 2007
Stamp Date	July 5, 2007
PDUFA Goal Date	May 5, 2007
Clinical Reviewer Name	Joette M. Meyer, Pharm.D.
Review Completion Date	April 25, 2008
Established Name	Levofloxacin
Trade Name	Levaquin®
Therapeutic Class	Quinolone Antibacterial
Applicant	Johnson & Johnson Pharmaceuticals
Priority Designation	S
Formulation	Tablets, Oral Solution, and Injection
Dosing Regimen	8 mg/kg BID (not to exceed 250 mg per dose) for 60 days
Indication	Inhalational Anthrax (Post- Exposure)
Intended Population	Children \geq 6 months of age

1 BACKGROUND

The safety and efficacy of levofloxacin for use in the prophylaxis of inhalational anthrax in adults (NDA 20-634/S-035, NDA 20-635/S-035, and NDA 21-721/S-003) was approved on November 24, 2004. The approval was based upon the accelerated approval regulations (21 CFR 314 Subpart H) where plasma concentrations achieved in humans were used as the surrogate for clinical efficacy.

At the time of the adult approval, pediatric safety and efficacy studies were being conducted by the Applicant under their Pediatric Written Request (PWR). Thus, the sNDAs were administratively split and the adult indication was retained under the original sNDA numbers and approved on November 24, 2004. [REDACTED] (b) (4)

On December 20, 2006, upon completion of their pediatric studies, the Applicant submitted sNDA 20-634/S-043, NDA 20-635/S-046, and NDA 21-721/S-011 which contained the results of the safety and efficacy studies performed in response to the PWR.

An approvable letter for these sNDAs was issued on June 21, 2007 pending negotiation of labeling. Labeling was negotiated July through September 2007, and an approval letter was issued on September 11, 2007.

The current submissions contain proposed labeling and cross-references to NDA 20-634/S-035, NDA 20-635/S-035, and NDA 21-721/S-003 (approval for adult indication of inhalational anthrax) and NDA 20-634/S-043, NDA 20-635/S-046, and NDA 21-721/S-011 (pediatric safety and efficacy data). [REDACTED] (b) (4)

[REDACTED] (b) (4) sNDAs supplement numbers have been assigned (NDA 20-634/S-047, NDA 20-635/S-051, and NDA 21-721/S-015). These efficacy supplements were dated July 3, 2007.

There is no new clinical data to be reviewed. Please see the Clinical Review on file for the above mentioned approved sNDAs: for efficacy review see Clinical Review by Dr. Carl Krause for sNDAs 20-634/S-035, 20-635/S-035, and 21-721/S-003; for safety review see Clinical Review by Dr. Kassa Ayalew for sNDAs 20-634/S-043, 20-635/S-046, and 21-721/S-011.

2 CLINICAL STUDIES SECTION – INHALATIONAL ANTHRAX (SECTION 14.9)

The following information explains how the adult indication was supported.

The effectiveness of LEVAQUIN® for this indication is based on plasma concentrations achieved in humans, a surrogate marker considered likely to predict efficacy. 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 patients receiving oral and intravenous regimens [see *Indications and Usage* (1.13); *Dosage and Administration* (2.1)].

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 $\mu\text{g}/\text{mL}$, respectively; and the corresponding total exposure is 47.9 ± 6.8 and 48.3 ± 5.4 $\text{mcg}\cdot\text{h}/\text{mL}$, respectively.

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.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD_{50} ($\sim 2.7 \times 10^6$) spores (range 17 - 118 LD_{50}) 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 steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/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.

3 APPROVED PEDIATRIC USE LABELING (SECTION 8.4)

The following pediatric safety information based upon the studies conducted under the PWR was added labeling to the Specific Populations, Pediatric Use (Section 8.4) on

September 11, 2007. No pediatric pharmacokinetic information was added to Clinical Pharmacology, Pharmacokinetics (Section 12.3) at that time.

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

^aNon-Fluoroquinolone: ceftriaxone, amoxicillin/ clavulanate, clarithromycin

^b2-sided Fisher's Exact Test

^cThere 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.

4 APPLICANT'S PROPOSED PEDATIRC ANTHRAX DOSING REGIMEN

The Applicant conducted a population pharmacokinetic (PK) analysis using pharmacokinetic data in children 6 months to 16 years from eight Phase 1 studies (five adult and three pediatric studies) and a Phase 3 study for the treatment of community-acquired pneumonia (CAP). In all three pediatric Phase 1 studies a single 7 mg/kg IV dose was administered. In the CAP study (LOFBIV-PCAP-003) children 6 months to 5 years of age received oral or IV levofloxacin 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.

Based upon the above information and matching the systemic exposure in adults who are receiving a dose of 500 mg once daily, the Applicant proposed the following dosage regimen:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

5 PHARMACOMETRICS REVIEW

The Pharmacometrics (PM) Group in the Office of Clinical Pharmacology evaluated the Applicant's population pharmacokinetic analysis and dosing recommendations and concluded that the Applicant's proposed dosing regimen of [REDACTED] (b) (4)

After concluding that the Applicant's population PK analysis was not adequately performed, the PM reviewer performed a new population PK analysis. The new model constructed by the PM reviewer included PK data from three Phase 1 studies children and two in adults (5 studies total, compared to 8 studies used by the Applicant). The PM reviewer did not include three of five adult PK studies used the Applicant because he concluded that the two studies which assessed bioavailability had the most robust data. In addition, the PM reviewer did not include the Phase 3 CAP study in the model.

The PM reviewer states:

The sparse samples taken in the Phase III study in pediatrics for treatment of community-acquired pneumonia (CAP) were not included in the reviewer's analysis, since the data did not support calculating clearance by non-compartment methods or by population PK methods due to shrinkage

towards the population mean...The Phase III data might have been possible to use for the reviewer's analysis if a new population PK model had been developed but due to time constraints and the fact that an adequate number of young (i.e. below 1 year) pediatric patients with rich PK sampling is available from the phase I trials, it was decided not to use the Phase III data for this analysis.

In a separate analysis, the PM reviewer evaluated the observed PK data from the Phase 3 CAP study in order to confirm that it was consistent with the predicted concentrations determined by the new model (which is discussed further below). In the CAP study, children 6 months to 5 years of age received 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. The PM reviewer concluded that the new model captured the observed C_{max} (about 10 μ g/mL) and C_{min} (about 0.6 to 0.1 μ g/mL for twice and once daily dosing, respectively) reasonably well, was similar to the predictions that the Applicant obtained using their own model, and is greater than the mean C_{max} in adults (6.5 μ g/mL) following 500 mg once daily. Therefore, the PM reviewer felt that the observed data from the CAP study were consistent with the predictions of new model. However, due the nature of the data (sparse sampling technique) it was not included in the model along with the data from the five Phase 1 trials which used a rich sampling technique. Finally, it should be noted, as discussed above, that doses of 10 mg/kg twice or once daily do not match the AUC values in adults obtained with the 500 mg dose. Therefore, the new model is necessary in order to find a new dosing regimen which more closely matches the AUC in adults. In addition to AUC, the PM reviewer used the new model to find a dosing regimen which also matched the C_{max} and C_{min} in children to adults, as discussed below.

Using the new model constructed with data from only the five Phase 1 studies, the PM reviewer first predicted the steady state AUC_{0-24} for a 15 mg/kg/day dose (selected because it would simplify pediatric dosing and still reasonably match adult exposure). The results by body weight and age are plotted in Figure 1 taken from the review. The predicted pediatric AUC was found to match that observed in adults taking 500 mg one daily in all dosing groups.

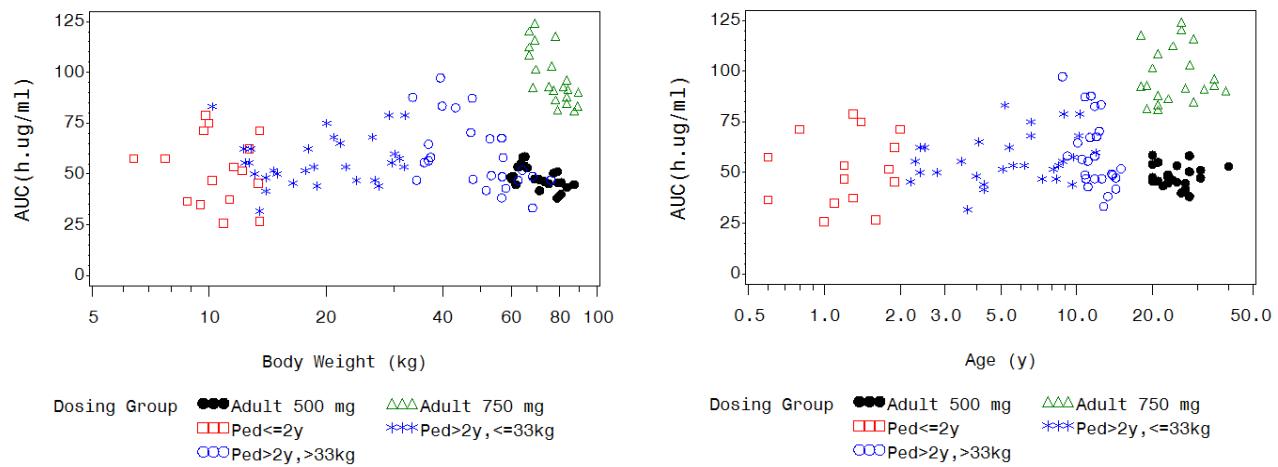


Figure 1: Predicted steady state AUC following 15 mg/kg levofloxacin (not exceeding 500 mg) vs. Body Weight and Age.

Next the PM reviewer attempted to match C_{max} in pediatrics to that observed in adults. The C_{max} in pediatrics should not exceed the adult values (for reasons related to safety effects on bone and joints) while the values of C_{min} should be maintained above the MIC of the organism to ensure efficacy. Dividing the 15 mg/kg/day dose into two doses of 7.5 mg/kg was found to achieve C_{max} values close to what was observed in adults following a 500 mg once daily dose, as shown in Figure 14.

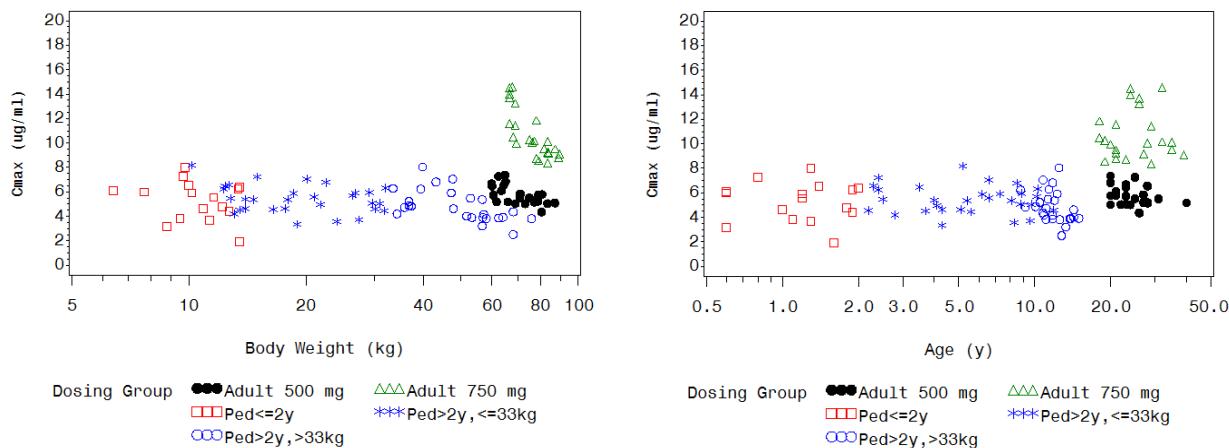


Figure 2: Predicted steady state C_{max} following 7.5 mg/kg b.i.d levofloxacin (not exceeding 250 mg) vs. body weight and age.

For larger children who weigh more than 50 kg, it was found that a 500 mg once daily dose was acceptable, as indicated by the plot of steady state C_{max} vs. body weight and age in Figure 15 (see black crosses).

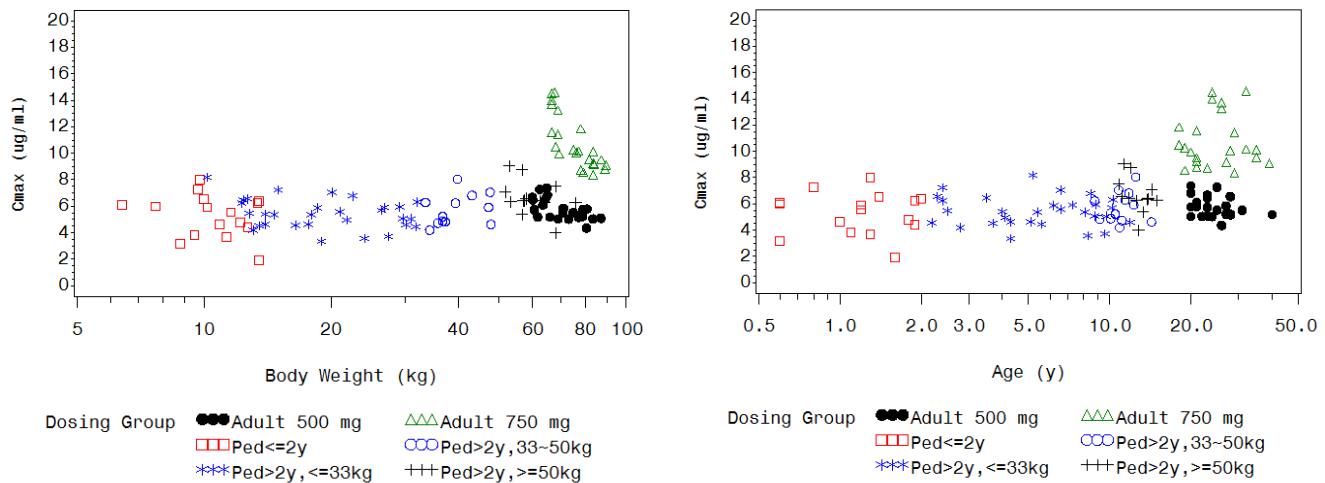


Figure 3: Predicted steady state C_{\max} vs. body weight and age following 7.5 mg/kg b.i.d levofloxacin (not exceeding 250 mg) in pediatrics less than 50 kg and 500 mg q.d. in patients 50 kg and above.

Next, a plot of the predicted steady state trough concentration (C_{\min}) of levofloxacin was constructed (Figure 4) suggesting that the twice daily dosing regimen will achieve C_{\min} values much higher than those observed in adults with 500 mg once daily of levofloxacin, making the minimum plasma concentrations much higher than the MIC.

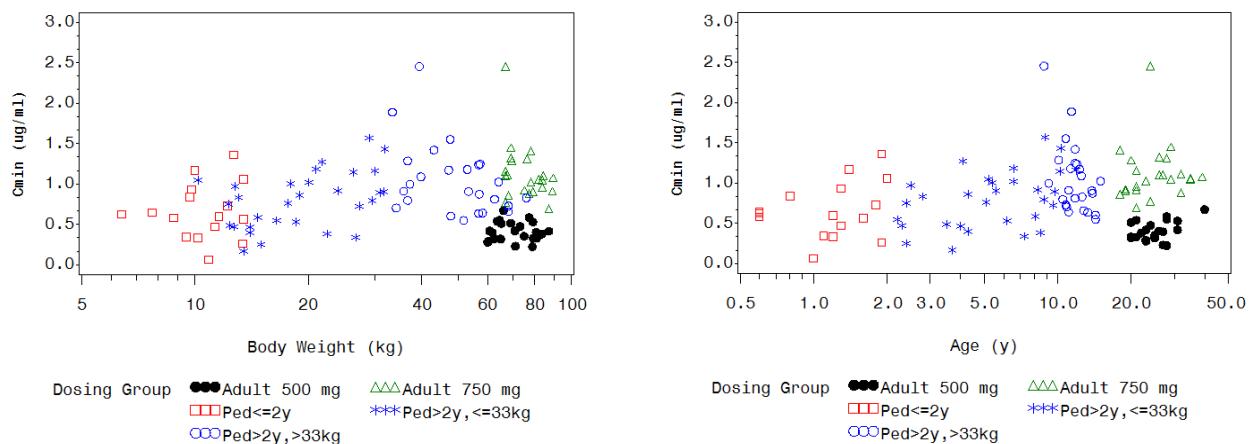


Figure 4: Predicted steady state C_{\min} following 7.5 mg/kg b.i.d levofloxacin (not exceeding 250 mg) vs. body weight and age.

As shown below in Table 3 and Figure 17, the 7.5 mg/kg twice daily dose (not to exceed 250 mg/dose) gives better results across all age groups than the Applicant's (b) (4)

Table 2: Comparison of predicted steady state AUC, C_{max} and C_{min} in pediatrics following dosing regimens of FDA and Sponsor. Data are presented as median (10th percentile to 90th percentile).

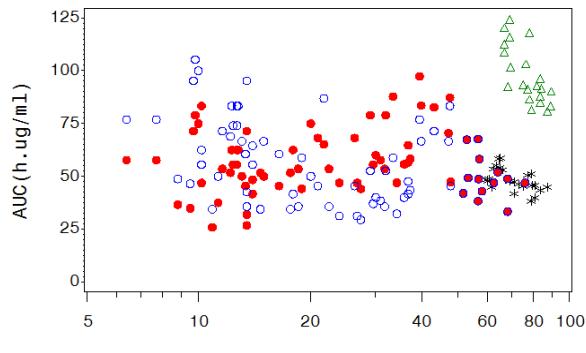
PK parameters	Dosing Regimen	6m to <2 y	2 to <5 y	5 to <10 y	10 to 18y	Adult 500 mg q.d.	Adult 750 mg q.d.
AUC _{ss,0-24} (μg.h.mL)	FDA	51.7 (26.8-75)	50 (41.7-65.2)	55.6 (46.9-83.3)	55.7 (42.0-83.5)	47.7 (41.8-55.1)	93.3 (83.4-124.3)
	Sponsor	69.0 (35.7-100)	66.7 (55.6-87.0)	37.0 (31.2-55.6)	47.6 (38.3-67.7)		
C _{max,ss} (μg/mL)	FDA	5.6 (3.2-7.3)	5.4 (4.2-6.6)	5.4 (3.7-7.1)	6.3 (4.6-8.1)	5.5 (5.0-6.8)	10.1 (8.7-14.0)
	Sponsor	7.4 (4.2-9.7)	7.2 (5.6-8.8)	6.2 (4.2-8.6)	6.5 (4.9-9.8)		
C _{min,ss} (μg/mL)	FDA	0.6 (0.26-1.2)	0.6 (0.25-1.1)	0.9 (0.38-1.6)	0.6 (0.2-1.4)	0.4 (0.3-0.55)	1.1 (0.86-1.4)
	Sponsor	0.8 (0.35-1.6)	0.7 (0.34-1.4)	0.2 (0.02-0.44)	0.3 (0.13-0.53)		

FDA: 7.5 mg/kg b.i.d not exceeding 250 mg/dose, 500 mg q.d. for peds over 50 kg

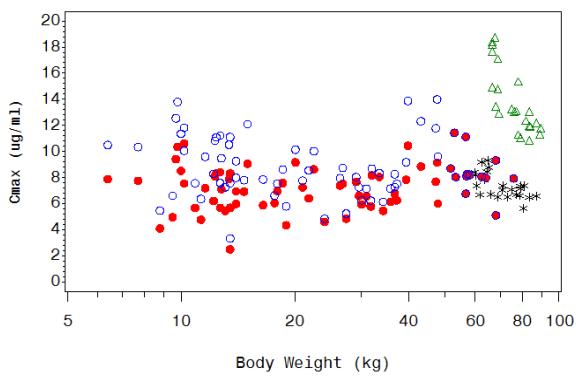
Sponsor: 10 mg/kg b.i.d for peds <5y, 10 mg/kg q.d. for peds >=5y, not exceeding 500 mg/dose

Adult 500 mg q.d.: based on observed data in study LOFBO-PHIO-097

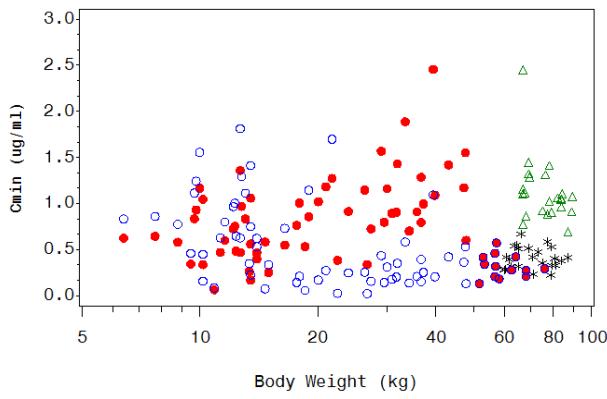
Adult 750 mg q.d.: based on observed data in study LOFBO-PHI-108



Stratified by: ***Adult 500 mg ▲▲Adult 750 mg
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Stratified by: ***Adult 500 mg ▲▲Adult 750 mg
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Figure 5: Scatter plot of steady state AUC, C_{max}, and C_{min} vs. body weight following FDA and Sponsor dosing regimen.

Therefore, based on the results of the PM analyses, as discussed above, the PM reviewer proposed that the pediatric dosage regimen for inhalational anthrax (post-exposure) matching the adult exposure following 500 mg once daily should be:

≥ 6 months: 7.5 mg/kg twice daily (not to exceed 250 mg/dose)

2-6 months: 5.0 mg/kg twice daily

Children > 50 kg may receive the adult dose of 500 mg once daily.

Although the PM reviewer determined a dose for children less than 6 months of age, it was decided that the clinical safety data did not support dosing children less than 6 months of age (i.e., the Phase 3 clinical studies enrolled children 6 months of age and older) and that only doses in children 6 months and older would be provided in labeling.

In addition, it was decided for convenience purposes (i.e., to prevent medication errors that could occur with transposition of the decimal point) the dose should be rounded up to 8 mg/kg twice daily (not to exceed 250 mg/dose) in children ≥ 6 months of age. The rounded up dose would primarily effect children below 31 kg, at which body weight they would be converted to the 250 mg dose. The PM reviewer stated that the model would also support the recommendation of an 8 mg/kg dose.

6 CONCLUSIONS AND REGULATORY RECOMMENDATIONS

The current submission does not contain any new pediatric information. The efficacy of levofloxacin in children for inhalational anthrax (post-exposure) is supported by plasma concentrations, a surrogate marker considered likely to predict efficacy. Using data from five Phase 1 studies (three in pediatrics and two in adults) a population PK analysis was performed by the Agency to identify the systemic exposure in children that would match the systemic exposure in adults who receive levofloxacin 500 mg once daily. The mean plasma concentrations of levofloxacin achieved with a 500 mg dose once daily in adults were previously shown to be associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax (sNDAs 20-634/S-035, 20-635/S-035, and 21-721/S-003).

Based upon the results of the Agency's population PK analysis, the proposed levofloxacin pediatric dosage regimen for inhalational anthrax (post-exposure) matching the adult exposure following 500 mg once daily is: 8 mg/kg twice daily (not to exceed 250 mg/dose) for children at least 6 months of age and older. Children > 50 kg may receive the adult dose of 500 mg once daily.

An approval is recommended for levofloxacin for inhalational anthrax (post-exposure) in children at least 6 months of age and older using a dose of 8 mg/kg twice daily (not to exceed 250 mg/dose). Children > 50 kg may receive the adult dose of 500 mg once daily. The label should be updated to include the revisions discussed in Section 7.

7 SUMMARY OF LABELING CHANGES

The label was revised to include the pediatric indication and dosing for inhalational anthrax (post-exposure) as well as to warn of the potential musculoskeletal effects of the drug in children.

The following is a summary of the labeling changes by PLR section:

1 INDICATIONS AND USAGE

The inhalational anthrax (post-exposure) indication was expanded to include children and a cautionary statement was added regarding the actual duration of therapy that has been studied (14 days):

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 likely to predict efficacy. 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 DOSAGE AND ADMINISTRATION

The adult dosing table (Table 1) was revised to include dosing for pediatric patients > 50 kg (i.e., 500 mg once daily). In addition, a cautionary statement was added regarding the actual duration of therapy that has been studied (14 days).

A new subsection (2.2 Dosage in Pediatric Patients) was added containing the following dosing chart:

Type of Infection ¹	Dose	Freq. Once every	Duration ²
Inhalational Anthrax (post-exposure) ^{3,4}			
Pediatric Patients (\geq 6 months, but < 50 kg)	8 mg/kg (not to exceed 250 mg per dose)	12hr	60 days ⁵

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 children for durations of therapy beyond 14 has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in children (See **Warnings and Precautions (5.7), Use in Specific Populations (8.40, and Clinical Studies [14.9])**). Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk.

5 WARNINGS AND PRECAUTIONS

Section 5.8 “Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals” was revised to indicate that levofloxacin is indicated in pediatrics for prevention of inhalational anthrax (post-exposure), but that “An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendonopathy, and gait abnormality) compared to controls has been observed” in children treated with levofloxacin.

8 USE IN SPECIFIC POPULATIONS

The following additional information was added to Section 8.4 (Pediatric Use):

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]*)

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]*).

12 CLINICAL PHARMACOLOGY

An additional subsection on pediatric pharmacokinetic information in children was added to Section 12.3 (Pharmacokinetics):

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 demonstrated that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age will 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.

14 CLINICAL STUDIES

Section 14.9 “Inhalational Anthrax (Post-Exposure)” was revised to include the pediatric indication and to include the predicted pediatric PK information from the population PK analysis:

The effectiveness of LEVAQUIN[®] for this indication 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 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 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 (AUC₀₋₂₄) 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 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 compared to controls has been observed (arthralgia, arthritis, tendonopathy, gait abnormality). 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. Steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL. Mean steady state AUC₀₋₂₄ was 33.3 mcg·hr/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.

17 PATIENT COUNSELING INFORMATION

A new bullet was added regarding musculoskeletal effects in children:

- **Musculoskeletal Disorders in Children:** 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 muscle or joint-related problems that occur during or following LEVAQUIN® therapy (*See Warnings and Precautions [5.7] and Use in Specific Populations [8.4]*).

Patient Package Insert

The following sentence was added under the section “Who should not take LEVAQUIN®?

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

Also, the follow question and answer was added:

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. In general, LEVAQUIN® is not recommended for children; however, it is approved for use in patients younger than 18 years old for anthrax exposure. 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.

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