

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**020634Orig1s061, 020635Orig1s067,
021721Orig1s028**

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 11, 2012
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 20634/S-061, NDA 20635/S-067, and NDA 21721/S-028
Applicant	Janssen Pharmaceuticals, Inc.
Date of Submission	October 27, 2011 (Received October 28,2011)
PDUFA Goal Date	April 28, 2012
Proprietary Name / Established (USAN) names	Levaquin [®] (Levofloxacin)
Dosage forms / Strength	Tablets (250 mg, 500 mg and 750 mg), Oral Solution (25 mg/mL), and Intravenous Solution (25 mg/mL Concentrated solution and 5 mg/mL in 5% Dextrose Premix)
Proposed Indication	Pneumonic Plague (Post-Exposure)
Recommended:	Approval

1. Introduction

These efficacy supplements for levofloxacin are being submitted by Janssen Pharmaceuticals, Inc. to support a new indication for treatment of pneumonic plague. Since pneumonic plague is an exceedingly rare infection, making human studies of the condition infeasible; the efficacy of levofloxacin was evaluated in an animal model. These NDA efficacy supplements were submitted for approval under 21 CFR 314 Subpart I – Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. This memo will mainly address the basis for approval of levofloxacin for treatment of pneumonic plague under the provisions of Subpart I.

2. Background

Levaquin[®] (Levofloxacin) is a fluoroquinolone antibacterial first approved for US marketing in 1996. The current labeling for levofloxacin includes indications for treatment of a variety of infections, including nosocomial and community-acquired pneumonia. Levofloxacin is also indicated for inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. Levofloxacin and other fluoroquinolones have known risks of adverse reactions described in product labeling. These descriptions include boxed warnings of the risks of tendinitis/tendon rupture, and exacerbation of myasthenia gravis. Other warnings include hypersensitivity, hepatotoxicity, central nervous system effects, peripheral neuropathy, phototoxicity and blood glucose disturbances. The product labeling includes a medication guide describing the adverse reactions associated with levofloxacin and the other fluoroquinolones.

Yersinia pestis is the causative pathogen of plague, and is considered a CDC category A bioterrorism agent. Naturally-occurring plague most commonly manifests in the bubonic form, but is an extremely rare condition in the United States. In a bioterrorism event, mass aerosol exposure to *Y. pestis* is expected to cause pneumonic and septicemic plague, conditions with a high fatality rate despite antibacterial treatment. However, pneumonic and septicemic plague are so rare that studies of the effectiveness of antibacterial drugs for these conditions are not feasible, and deliberate exposure of humans to *Y. pestis* would not be ethical.

The National Institute of Allergy and Infectious Diseases (NIAID) conducted development work on an animal model of pneumonic plague to evaluate the effectiveness of antibacterial drugs for treatment of pneumonic plague. The development work for this animal model included four studies (i.e., natural history studies) conducted at three different facilities evaluating the effects of exposure to aerosolized *Y. pestis* in African green monkeys (AGM). The above-described work was conducted under an IND held by NIAID, and ultimately led to the levofloxacin efficacy study submitted in this application. Based on the review of these AGM studies and the comparison of disease in AGM with reports of human cases of pneumonic plague, the AGM model was considered sufficiently well characterized for predicting response in humans.

3. CMC/Device

The CMC review by Dr. Dorota Matecka consisted of acceptance of the applicant's request for categorical exclusion from environmental assessment. The reviewer recommended approval. No new CMC information was submitted in these efficacy supplements for levofloxacin; no changes to the approved formulations of levofloxacin were proposed.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Dr. Amy Nostrandt. She recommended approval of the efficacy supplement. Her review described the findings of the four natural history studies of aerosolized *Y. pestis* exposure in AGM, three studies of the pharmacokinetics of levofloxacin in AGM, and the efficacy study of levofloxacin for treatment of pneumonic plague in AGM. Dr. Nostrandt's review also discussed the associated independent pathology and radiology reports conducted for these AGM studies.

As described in the pharmacology/toxicology review, AGM in the natural history studies were exposed to target aerosol concentrations of *Y. pestis* via head only exposure. This head-only exposure resulted in actual challenge doses ranging from 3 to 1150 times the median lethal dose (LD₅₀) determined from a prior study. Animals challenged with $\geq 20 \times$ LD₅₀ in the natural history studies consistently developed disease. Telemetry was used to monitor fever and heart rate in AGM. Respiratory rate was also measured. Blood samples were obtained for blood cell counts and blood cultures, and radiographs were obtained in some of the studies.

The natural history studies showed that AGM exposed to $\geq 20 \times LD_{50}$ developed fever and bacteremia within 2-3 days after exposure, followed by death or euthanasia within 2-9 days after exposure. Most AGM died or were euthanized *in extremis* on days 3 or 4.

Post-mortem findings included evidence of lung pathology (pleural effusions, edema of the mediastinum and/or lungs, or focal red-purple discoloration of nodules/masses in the lungs); the nodules correlated microscopically with areas of suppurative hemorrhage, inflammation and edema. Bacteria were also visible microscopically in the alveoli and/or in macrophages. In some AGM, severe lung lesions had progressed to parenchymal necrosis. Additional tissues investigated post-mortem in all four studies included liver, brain, and lymph nodes. Dissemination of bacteria to these other tissues (occasionally to the brain) was found. Lymph nodes showed similar pathology to the lung in some animals. Similar findings were seen in the spleen in some animals where post-mortem evaluation of this organ was conducted.

The results from the pharmacokinetic and efficacy studies are discussed in other sections of this memo. Overall, it appeared that the pharm/tox reviewer agreed with the findings from the AGM studies as described in the study reports.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Dr. Seong H. Jang. The focus of the clinical pharmacology review was the basis for the humanized dose of levofloxacin chosen to be used in the AGM efficacy study, and the dose recommendations for adult and pediatric patients. The dose of levofloxacin used in the study of AGM was an initial 8 mg/kg dose given in a 30-minute intravenous infusion followed by an additional 30-minute IV infusion of 2 mg/kg given 12 hours later. This 8/2 mg/kg dose regimen in AGM was a “humanized” dose regimen designed to provide a comparable plasma concentration-time profile to that in adult humans receiving a 500 mg IV dose once daily. Pediatric PK studies of levofloxacin were previously reviewed in an earlier supplement. This earlier review concluded that a dose regimen in pediatric patients (≥ 6 months of age and < 50 kg) of 8 mg/kg twice daily (not to exceed 250 mg/dose) provided comparable systemic exposure to adults given 500 mg once daily. For pediatric patients > 50 kg, the adult dose regimen should be used. No pharmacokinetic or safety data were available for making a dose recommendation for pediatric patients < 6 months of age.

Given the efficacy of the “humanized” dose regimen in the AGM study, the reviewer recommended a dose regimen of 500 mg once daily for adults and pediatric patients > 50 kg. For pediatric patients ≥ 6 months of age and < 50 kg, the recommended dose regimen is 8 mg/kg given twice daily (not to exceed 250 mg/dose). The reviewer agreed with the approval of these levofloxacin efficacy supplements, and no phase 4 commitments were recommended.

6. Clinical Microbiology

The clinical microbiology review was conducted by Dr. Simone Shurland. The reviewer recommended approval of these efficacy supplements for levofloxacin. Levofloxacin is a fluoroquinolone antibacterial drug with a known mechanism of action. The *in vitro* testing of 189 *Yersinia pestis* isolates from 5 different studies showed a range of minimum inhibitory concentration (MIC) values of <0.03 to 0.12 mcg/mL.

The review also discussed the findings from the levofloxacin efficacy study in AGM, and challenge studies in mice and rats. The mice and rat studies showed that intraperitoneal administration of levofloxacin to these animals provided a survival advantage over control treatment after aerosol exposure to *Y. pestis*. The efficacy results from the AGM study are discussed in the next section of this memo. It is noted that a specific *Y. pestis* CO92 strain was used in all the animal model studies. This strain has an MIC for levofloxacin of 0.03 mcg/mL across all laboratories conducting testing. The reviewer also provided labeling recommendations for the microbiology section of labeling, including susceptibility breakpoints identifying all strains with MIC \leq 0.25 mcg/mL as susceptible. This susceptibility value is based on the range of MIC values for levofloxacin reported in the literature. No breakpoints for intermediate or resistant could be set from the available data.

(CDTL Comment: While one limitation of the animal model study is the use of a single Y. pestis isolate with a low MIC for levofloxacin, the higher MIC for the susceptibility breakpoint is still a reasonable choice. In the animal efficacy study, the average AUC/MIC for levofloxacin was almost 400 mcg-h/mL, a value well in excess of that considered necessary for activity of the fluoroquinolones. This suggests that levofloxacin is still likely to be active against organisms with an MIC at the upper end of the MIC range for levofloxacin.)

7. Clinical/Statistical- Efficacy

The medical officer review of the levofloxacin efficacy study was conducted by Dr. Elizabeth O'Shaughnessy. The statistical review of this animal efficacy study was conducted by Dr. Xianbin Li. A separate review of the natural history studies and their comparison to human plague cases was written by Dr. Yuliya Yasinskaya. The reader is referred to these reviews for details regarding their clinical and statistical findings.

Dr. Yasinskaya concluded that the AGM model of plague is sufficiently well-characterized with regard to the pathogenic agent (*Y. pestis*) and the pathophysiology of disease. She also agreed with the proposed design of the AGM efficacy study. The one limitation identified by Dr. Yasinskaya is uncertainty about the correlation between the proposed trigger for intervention (fever) and the presence of bacteremia. The presence of bacteremia at the time of trigger could not be definitively determined from the natural history data, but it was expected to be determined in the efficacy study whether AGM would be bacteremic at the time of levofloxacin treatment.

Dr. O'Shaughnessy recommended approval of the efficacy supplements for levofloxacin. Dr Li concluded that the efficacy of levofloxacin in the treatment of pneumonic plague in AGM was supported by this animal study. The efficacy of levofloxacin for treatment of plague is based on the efficacy study in the African green monkey model of pneumonic plague. In the study, telemetrized and catheterized AGM were exposed to an aerosol of *Y. pestis* CO92 strain with a targeted aerosol exposure of 100 ± 50 LD₅₀. The primary endpoint of this trial was survival at day 28 after exposure; the trial was investigator-blinded in that the veterinarian assessing animals for euthanasia was blinded to treatment assignment. In three cohorts, AGM were randomized to treatment with levofloxacin or placebo. Fever in each individual animal, defined as mean temperature $>39^{\circ}\text{C}$ for one hour, was used as the trigger for treatment initiation. All animals were treated within 5 hours of meeting the definition for fever. Animals in the levofloxacin group received 8 mg/kg of levofloxacin in a 30-minute IV infusion followed by a 2 mg/kg dose in a 30 minute infusion 12 hours later. Control animals received matching placebo infusions. The duration of study drug treatment was 10 days.

In the primary analysis population, there were 17 AGM treated with levofloxacin, and 7 control animals. All 7 control animals died or were euthanized by Day 5 after aerosol exposure (0% survival). In the 17 levofloxacin-treated animals, there was one death (94% survival at day 28). The difference in survival rates between treatment groups was statistically significant (p-value $< .0001$). The treatment failure in the levofloxacin group was an animal that survived to day 9 of treatment, but developed vomiting due to an ill-defined stomach problem. Since it can not be determined conclusively whether the *Y. pestis* infection contributed to the stomach condition, it is reasonable to include this animal in the analysis as a treatment failure.

One animal was excluded from the levofloxacin group after randomization for a deviation from protocol. This animal was treated with levofloxacin prior to meeting criteria for fever. This animal survived, although it received only the 8 mg/kg initial dose of levofloxacin, and a partial dose several days later. Therefore, exclusion of this animal from the analysis is conservative. Another animal that was randomized to levofloxacin treatment became ill; it was not given the aerosol challenge with *Y. pestis* and did not receive levofloxacin treatment. Even if both of these animals were included in the endpoint analysis as treatment failures, the difference in survival rates between treatment groups would be statistically significant. The medical review includes several subgroup analyses, evaluating survival in bacteremic animals, survival in animals that received an aerosol challenge ≥ 20 LD₅₀, and survival in animals with radiographic evidence of disease. In these subgroups, the differences in survival rates between treatment and control groups remained statistically significant.

Notable findings from the study were seen in post-mortem examinations of three levofloxacin-treated animals. Animals that survived to day 28 (all were treated with levofloxacin) were sacrificed at that time for pathological examination. The notable findings were the growth of *Y. pestis* from culture of lung tissue (302 CFU/g) in one animal (X523), from both lung tissue (177 CFU/g) and terminal blood culture (7 CFU/mL) in another animal (X648), and from a terminal blood culture (3 CFU/mL) only. These findings are described in greater detail in the clinical review. Control animals did show much higher concentrations of *Y. pestis* on had

terminal blood (10^4 to 10^5) and lung tissue cultures (10^7 to 10^{10}) than was seen in these levofloxacin-treated animals.

In addition to the animal model study, levofloxacin is approved for treatment of nosocomial and community-acquired pneumonia. Levofloxacin is effective for treatment of humans with infections of the lungs due to other bacterial pathogens, and the dose used in humans provides the same or greater drug exposure than that in AGM in the animal model. This known effectiveness of levofloxacin in human lung infections, along with the evidence of reduced mortality with levofloxacin treatment in AGM with pneumonic plague, provides the basis for concluding that levofloxacin is reasonably likely to reduce mortality in the treatment of humans with plague.

8. Safety

No new information regarding safety was included in these efficacy supplement submissions. Levofloxacin was first approved for marketing in the US in 1996, and its safety profile is well known from clinical trials and postmarketing experience. The current labeling accurately describes the known adverse reactions associated with levofloxacin. Although there are several severe adverse reactions associated with levofloxacin use, the benefits of treatment for plague (to reduce the risk of mortality) outweigh the risks of levofloxacin treatment.

9. Advisory Committee Meeting

Advisory committee meetings were held on the morning of April 3, 2012 to consider the animal model for pneumonic plague, and on the morning of April 4, 2012 to consider the levofloxacin efficacy supplement for treatment of pneumonic plague. In the April 3, 2012 session, the committee was not asked to comment on the similarities and differences between the AGM model of pneumonic plague and human disease. The committee members agreed that there were minimal differences between the AGM model and human disease. The committee seemed to agree that the AGM model was well characterized. The committee was also asked about the trigger for treatment in the AGM model. The committee members seemed to support the use of fever as a trigger for treatment in the animal model, agreeing that fever was correlated with disease progression and appeared to have the least variability of potential triggers discussed.

At the April 4, 2012 session, the committee was asked to vote on whether the animal model results provide substantial evidence for effectiveness of levofloxacin for treatment of humans with pneumonic plague. The committee members unanimously agreed that the animal model results provided substantial evidence for the effectiveness of levofloxacin for treatment of humans with pneumonic plague. The committee members gave favorable comments about the animal model study results for levofloxacin. Some committee members expressed concerns about the persisting *Y. pestis* growth on post-mortem examination of some animals, asking

whether susceptibility testing for levofloxacin could be performed on these isolates. However, these concerns about the persisting growth did not prevent the members from concluding that levofloxacin would be beneficial in treatment of humans with plague. The committee was also asked about whether they had any additional recommendations for safety evaluation in humans. The committee members agreed that the available safety information from clinical studies and post-marketing for levofloxacin were sufficient. The only comment regarding additional studies was the suggestion to explore whether additional information (PK and safety) could be obtained for pediatric patients less than 6 months of age, whether from the literature or additional studies.

10. Pediatrics

For these efficacy supplements for levofloxacin, efficacy data for treatment of AGM is being extrapolated to adult humans with plague. A similar extrapolation of the AGM study results to pediatric patients with plague is also reasonable. Although there is limited information available about human cases of plague, plague (whether bubonic, pneumonic, or septicemic) is expected to have similar pathophysiology in both adults and pediatric patients. Most cases of naturally-occurring plague in the literature are bubonic; this is true of all age groups. FDA has previously allowed extrapolation of adult efficacy for antibacterial products for treatment of pneumonias to pediatric patients, because of the similar pathophysiology and expected response to treatment. Levofloxacin is approved for treatment of pediatric patients 6 months of age and older with inhalational anthrax (post-exposure), based on safety and pharmacokinetic data that has previously been reviewed by FDA. However, no data are available to address safety or pharmacokinetics of levofloxacin in pediatric patients younger than 6 months of age.

The division met with the pediatric review committee (PeRC) on March 14, 2012. In this discussion, the PeRC agreed with the division's proposal for extrapolation from animals to pediatric patients 6 months of age or older, in a similar fashion to what was being done for adults. The PeRC also agreed that waiver of pediatric studies for the pediatric population less than 6 months of age was appropriate. This waiver is based on concerns about the potential safety issues with fluoroquinolones (as described in labeling) and because safety and pharmacokinetic studies of levofloxacin in pediatric patients younger than six months of age would be infeasible. Since other options are commonly used for treatment of pediatric patients in this age group, the use of levofloxacin in this age group would be too rare to be studied. The proposed indication for plague is also too rare a condition to expect that pediatric patients younger than six months of age with this condition could be studied.

11. Other Relevant Regulatory Issues

Since there were no clinical studies conducted, the financial disclosure requirements for clinical investigators do not apply to these efficacy supplements. There were inspections

as well as sites where pharmacokinetic studies of levofloxacin in AGM or methods validation procedures were conducted. The reader is referred to establishment inspection reports by Dr. Zhou Chen and Dr. Abhijit Raha for details of the inspectional findings. The recommended classification for all the inspections was “voluntary action indicated”. The inspectional findings did not raise concerns about the results for the natural history or efficacy studies in the AGM model. However, the inspections did raise issues about the reliability of some of the pharmacokinetic sample results for levofloxacin in AGM. The clinical pharmacology review discusses how the inspectional findings for PK samples and quality control standards were addressed.

12. Labeling

Levaquin[®] is an approved drug product with labeling in the physician’s labeling rule (PLR) format. Proposed labeling included an indication for treatment of plague, including pneumonic and septicemic plague and for prophylaxis of plague. Proposed labeling also includes updates to the Medication guide and other sections of labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of these labeling supplements for levofloxacin. The animal model for pneumonic plague in African green monkeys (AGM) is sufficiently well-characterized to be relied upon as a single animal model for treatment of pneumonic and septicemic plague under 21 CFR 314 Subpart I. The animal efficacy study described in this memo, in addition to the known safety profile for levofloxacin and its known effectiveness for treatment of a variety of serious infections, establish that levofloxacin is reasonably likely to provide clinical benefit in humans with plague.

- Risk Benefit Assessment

Levofloxacin is a fluoroquinolone antibacterial approved for treatment of a variety of serious infections, including community-acquired pneumonia and nosocomial pneumonia. Levofloxacin has a well-known safety profile, including several serious adverse reactions described in the package insert and medication guide. The benefits of levofloxacin for treatment of these bacterial infections outweigh the known risks of levofloxacin treatment. Plague is a rare but serious infection; pneumonic and septicemic forms of plague, in particular, are serious conditions that are fatal in a high proportion of patients. The results of the

levofloxacin efficacy study in AGM show that early treatment of pneumonic or septicemic plague with levofloxacin reduces the risk of mortality. Overall, the benefits of treatment with levofloxacin for plague infections in humans outweigh the risks of levofloxacin treatment. For prophylaxis of plague, the available data suggest that asymptomatic individuals with significant exposure to aerosolized *Y. pestis* would be at high risk of development of infection and fatal outcome. Early treatment of asymptomatic individuals is preferable to waiting for the development of symptoms of disease; since delays of antibacterial treatment raises the risk of fatal outcome. Therefore, despite the known significant risks of levofloxacin treatment, the benefits of prophylaxis for plague in asymptomatic individuals exposed to aerosolized *Y. pestis* outweigh the risks of levofloxacin treatment.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None – A REMS program is not considered to be necessary for levofloxacin

- Recommendation for other Postmarketing Requirements and Commitments

Under 21 CFR 314 Subpart I, applicants are required to “conduct postmarketing studies, such as field studies, to verify and describe the drug’s clinical benefits and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises.”

Based on this regulatory requirement, the applicant should be required to submit a protocol for a field study to describe the safety and effectiveness of levofloxacin for treatment and prophylaxis of plague. This protocol should be prepared in advance, but could not be conducted unless mass exposure to aerosolized *Y. pestis* was to occur. I recommend that the protocol submission for this postmarketing requirement be required within a year of supplement approval. However, study start and study completion for this postmarketing requirement can not be specified, since they would rely on the occurrence of a mass exposure to aerosolized *Y. pestis*.

- Recommended Comments to Applicant

The recommendation for approval should be conveyed to the applicant. The applicant should be notified of the postmarketing requirement for a field study of levofloxacin for treatment and prophylaxis of plague.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J ALEXANDER
04/25/2012