CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Deputy Division Director's Decisional Memo

Date	April 22, 2012
From	Katherine Laessig, M.D.
Subject	Deputy Division Director's Decisional Memo
NDA #	sNDAs 20-634/S-061, 20-635/S-067, NDA 21-721/S-028
Applicant Name	Johnson and Johnson PRD on behalf of Janssen Pharmaceuticals
Date of Submission	10/28/2011
PDUFA Goal Date	4/27/2012
Proprietary Name / Established (USAN) Name	Levaquin® (levofloxacin)
Dosage Forms / Strength	Levofloxacin tablets, IV injection, oral solution
Approved Indications	Nosocomial pneumonia; community-acquired pneumonia; acute bacterial sinusitis; acute bacterial exacerbation of chronic bronchitis; complicated skin and skin structure infections; uncomplicated skin and skin structure infections; chronic bacterial prostatitis; complicated urinary tract infections; acute pyelonephritis; uncomplicated urinary tract infections; inhalational anthrax (post-exposure)
Proposed Indication	Plague in adults and pediatric patients ≥ 6 months of age
Action:	Approval

Material Reviewed/Consulted	**Names of discipline reviewers**
Cross Discipline Team Leader Review	John Alexander, M.D., M.P.H.
Clinical Review	Elizabeth O'Shaughnessy, M.D.
Pharmacology/Toxicology Review	Amy Nostrandt, D.V.M., Ph.D.
Clinical Pharmacology Review	Seong Jang, Ph.D.
Clinical Microbiology Review	Simone Shurland, Ph.D.
Biometrics Review	Xianbin Li, Ph.D.
OSI Reviews	Zhou Chen, M.D., Ph.D. Abhijit Raha, Ph.D.
DMPP Review	Robin Duer, M.B.A., B.S.N., R.N.
DDTCP Review	Adora Ndu

1.0 Background

Levofloxacin is a member of the fluoroquinolone class of antibacterial drugs and received marketing approval in 1996. It has activity against a wide range of Gram positive and negative organisms and acts via inhibition of DNA synthesis through the interaction of the drug complexes with one of both of the target bacterial type II topoisomerase enzymes, DNA gyrase and DNA topoisomerase IV. The topoisomerases play essential roles in bacterial DNA replication, transcription, recombination, and repair of DNA. These complexes trigger poorly defined events within the bacterial cell resulting in double-stranded DNA breaks, damage, and ultimately cell death. Levofloxacin is indicated for use in many serious bacterial infections at a variety of body sites, and has an accompanying Medication Guide to describe the known risks of the drug.

The applicant has submitted these supplements under 21 CFR 314.600 for New Drugs, which is commonly referred to as the Animal Rule, in support of the indication of plague. Plague is a serious and often fatal infection in humans that occurs in three forms: bubonic, septicemic, and pneumonic. Plague is caused by the Gram-negative coccobacillus *Yersinia pestis* (*Y. pestis*). Untreated septicemic and pneumonic plague is generally fatal. Fortunately, plague is extremely rare in current times, but *Y. pestis* has the potential to be used as an agent of bioterrorism. Because it is infeasible to study plague in humans due to its low prevalence, and unethical to expose humans intentionally, studies in animals are necessary to provide evidence of efficacy of treatment. These supplements contain the results of four natural history studies in the African Green Monkey (AGM), which are intended to support the AGM as an animal model sufficiently well-characterized for predicting the response in humans, a single efficacy study of levofloxacin for the treatment of plague in AGMs, as well as studies in small animal models of infection (mice and rats). As noted above, levofloxacin has multiple indications, and under 21 CFR 314.610, the data from these indications may also be considered supportive evidence. These supplements were granted a priority review and were presented at a meeting of the Anti-Infective Drugs Advisory Committee on April 4, 2012.

These submissions have been reviewed by pharmacology/toxicology, clinical pharmacology, clinical microbiology, clinical, and biometrics reviewers and this memo will summarize elements of their reviews by discipline. Note there is no new data on chemistry, manufacturing, and controls in these supplements. For detailed discussions by discipline, please refer to the respective reviews.

2.0 Summary of Pharmacology/Toxicology

Please refer to the review of Dr. Amy Nostrandt for additional information. She recommends approval of the supplements. Key findings from her review include:

- The four National Institute of Allergy and Infectious Diseases (NIAID) sponsored natural history studies in the African Green Monkeys (AGM) confirmed the lethality of aerosolized *Yersinia pestis*, the causative bacteria of plague, strain CO92 in the AGM documented the natural history of the disease in telemetered animals and identified fever as a clinical sign, i.e. trigger, for antibiotic intervention.
- In the AGM model, telemetered monkeys received a target dose of 100XLD_{50} (where 1 LD_{50}= colony forming units of *Y. pestis*) in a head-only aerosol chamber. Actual doses were calculated using sampling data from an all glass impinger in the aerosol chamber and from whole body plethysmography of the animals just prior to aerosol challenge. Actual challenge doses across the studies ranged from 3 to 1150 LD_{50}. Four studies were conducted in a total of 36 AGMs. Animals challenged with at least 20 LD_{50} developed disease.
- Fever and bacteremia were the most prominent features of disease and were established within 2-3 days. In general, tachypnea and tachycardia coincided with the onset of fever.
- Thoracic radiographs were obtained for some animals in two of the natural history studies. Independent review of the radiographs concluded that there was a common appearance and progression of the severity of changes over time. All animals exhibited pulmonary infiltrates that began as small infiltrates with local involvement early in the course of disease but progressed to multilobar opacities consistent with pnemonitis at the time of death.
- AGMs died or were euthanized between Day 2 and 9 post-challenge. The majority of AGMs died on Day 3 or 4. The animals underwent necropsy and macroscopic findings included pleural effusions, edema of the mediastinum and/or lungs, multiple focal areas of red to purple discoloration with nodules or masses in the lungs. Fibrin accumulation was noted in the lung. The most severe lung lesions had progressed to parenchymal necrosis. Bacteria were visible in alveoli and/or in macrophages.
- The independent reviewing pathologist concluded that there is a common pathology associated with lethal infection by inhaled *Y. pestis* strain CO92 in AGMs, based on these four studies. Post-challenge infection and dissemination were found to occur quickly in this species, with morphologic changes in the lung appearing to begin as lobar to sublobar serous and fibrinous exudates with intra-alveolar and intracellular bacteria along with increased numbers of alveolar macrophages. These changes observed in the lung were found to transition quickly to diffuse necrotizing pneumonia characterized by alveoli and airways filled with bacteria, inflammation and hemorrhage. There was dissemination of bacteria to bronchial/tracheobronchial and mediastinal lymph nodes, mediastinal connective tissue and spleen, initiating changes in the tissues such as hemorrhage, inflammation, and edema.

- Data from exploratory PK studies in AGMs were used to select a daily IV dosing regimen of 8 mg/kg followed by 2 mg/kg 12 hours later that mimics yet provides lower than human exposures at a 500 mg qd dose. This 8/2 mg/kg dosing regimen was used in the animal efficacy study.
- In the efficacy study, findings in control animals were consistent with those in the natural history studies. Treatment with levofloxacin was initiated in animals in the treatment group when a fever of 39ºC or more was sustained for over an hour. Under the conditions of study, levofloxacin administered for 10 days resulted in a 94% survival rate (16/17 AGMs) compared to 0% (0/7 animals) in the placebo arm.

3.0 Summary of Clinical Microbiology

Please refer to the review of Dr. Simone Shurland for additional information. She recommends approval of the supplements. Key findings from her review include:

- Levofloxacin has been shown to have *in vitro* activity against *Y. pestis* laboratory and clinical isolates with minimum inhibitory concentration (MIC) values that range from <0.03 to 0.12 mcg/mL. There were more than 189 isolates tested which were evaluated in five studies. There was no significant different in the MICs of the *Y. pestis* tested by biovar type (i.e. Antigua, Medievalis, Orientalis) or geographic region. There were no wild type *Y. pestis* isolates with an MIC greater than 0.12 mcg/mL.
- The *Y. pestis* CO92 strain, used in the pivotal efficacy study and the four natural history studies, had MICs of 0.03 mcg/mL across laboratories. This MIC value was similar to those observed among *Y. pestis* isolates sourced from various geographic regions.
- Several studies evaluated the activity of prophylactic and therapeutic levofloxacin in small animal models (mice and rats) of pneumonic plague. Overall, the results demonstrated that levofloxacin dosed once daily for six days at 5 to 15 mg/kg/d achieved 100% survival rates in both mice and rats without any noticeable toxic effects. Levofloxacin treatment initiated early, no later than 36 hours post-challenge in mice and 42 hours post-challenge in rats remained completely effective. However, when re-challenged with *Y. pestis*, levofloxacin-treated mice and rats behaved differently with the majority of mice dying and the majority of rats surviving. Levofloxacin was equally effective in neutropenic and non-neutropenic mice in the post-exposure murine model.
- The efficacy of levofloxacin in the treatment of pneumonic plague in AGMs was supported by the primary and sensitivity analyses in the treatment study, and will be discussed further in the section on clinical efficacy below.

4.0 Summary of Clinical Pharmacology

Please refer to the review by Dr. Seong Jang for further details on the clinical pharmacology information contained in these supplements. He recommends approval. Key findings from his review include:

- A PK simulation study with the PK parameters of levofloxacin obtained in AGMs demonstrated that a 30-minute IV infusion of 8 mg/kg followed by an additional 30-minute IV infusion of 2 mg/kg 12 hours later would provide AGMs with a levofloxacin plasma concentration-time profile comparable to humans receiving the 500 mg q d IV dose. Levofloxacin plasma concentrations in humans exceed the MIC against *Y. pestis* (0.03 mcg/mL) for the entire dosing interval following administration of 500 mg IV q d.
- In healthy AGMs that received the IV administration of the humanized dose of 8 mg/kg IV followed by 2 mg/kg IV 12 hours later, the plasma concentrations of levofloxacin did not exceed those observed in humans who received the 500 mg IV q d dose at any time during the 24 hour period. The humanized dose in healthy AGMs resulted in a Cmax of 3.3 mcg/mL and an AUC_{0-24} of 11.0 mcg•hr/mL, which were lower than the Cmax and AUC_{0-24} in humans by approximately 50% and 75%, respectively.
- The animal efficacy study demonstrated that levofloxacin is efficacious for the treatment of plague in the AGM model using the humanized dose and that the humanized dose used provided AGMs with a PK profile similar to humans while keeping the systemic exposure lower than that observed in humans receiving levofloxacin 500 mg IV q d.
- The plasma levofloxacin concentrations observed in cohort 3 of the efficacy study generally aligned with those observed in the PK study of healthy AGMs with Cmax of 3.3±0.82 vs. 3.3±0.27 mcg/mL, peak concentrations of 1.08±0.22 vs. 0.81±0.18 mcg/mL and trough concentrations of 0.07±0.03 vs. <0.03 to 0.06 mcg/mL, respectively.
- These data fulfill the criterion of the Animal Rule that data on product PK and PD in animals and humans allow selection of an effective human dose.

5.0 Summary of Clinical Efficacy

The efficacy data in these supplements has been reviewed by the biometrics reviewer, Dr. Xianbin Li, and the medical officer, Dr. Elizabeth O'Shaughnessy. For additional information, please refer to their respective reviews. Both of them, as well as the Cross Discipline Team Leader, Dr. John Alexander, recommend approval of these supplements.

As stipulated by the Animal Rule to ensure the applicability of animal data to human disease, the pathophysiology of the disease and the product's

mechanism of action must be reasonably well-understood, and efficacy must be demonstrated in more than one animal model, unless one animal model is sufficiently well characterized for predicting the response in humans. The pathophysiology of plague is reasonably understood, based on published literature, as is the mechanism of action of levofloxacin. The four natural history studies established that the AGM is an animal model that is sufficiently well characterized to predict response in humans, as concluded by Dr. Yuliya Yasinskaya, medical officer in DAIP, who reviewed the four natural history studies. Portions of her review are excerpted below.

The four natural history studies of plague in AGMs are as follows:

1. Natural Course of Untreated Pneumonic Plague in African Green Monkeys", Battelle Study Protocol 617-G607610
2. Natural Course of Untreated Pneumonic Plague in African Green Monkeys", Battelle Study 875-G607610
3. A Natural History Study of Inhalational Plague *Y. pestis* Strain CO92 in Adult Telemetered African Green Monkey", Lovelace Respiratory Research Institute (LRRI) Study Protocol FY06-126
4. A Natural History Study of Pneumonic Plague in African Green Monkey", U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) Study Protocol FY03-09G

Table 1 below illustrates summary findings from Dr. Yasinskaya's review of the natural history studies.

Table 1 Summary of Findings from the AGM Primary Pneumonic Plague Natural History Studies

Parameter	Battelle Study 617-G607610	Battelle Study 875-G607610	LLRI	USAMRIID
Aerosolized Dose of *Y. pestis* CO92 Strain	106 LD50 to 1150 LD50 3.59×10^4 to 3.91×10^5	24 LD50 to 88 LD50 8.24×10^3 to 2.98×10^4	44 LD50 to 255 LD50 1.5×10^4 to 5.6×10^4	9 LD50 to 57 LD50 3.1×10^3 to 1.9×10^4
Animals	3 males and 7 females	5 males and 5 females	5 males and 5 females	3 males and 3 females
Mortality	100% 10 found dead	100% 10 found dead	100% (3 found dead, 7 euthanized)	67% (4/6: 1 found dead, 3 euthanized)
Timing of Death (post-exposure)	63 hours (55 to 81 hours) estimated	93 hours (66 to 139 hours)	90 hours (72 to 100 hours)	112 h or 4.7 days (99.5 to 125 h)
Timing of Fever (T > 39°C)	34 hours (26 to 39 hours) estimated	55 hours (48 to 62 hours)	67 hours (52 to 80 hours)	73 h or 3 days (52 to 80 h)
Interval between Fever and Death	28 hours (17 to 42 hours)	38 hours (16 to 75 hours)	23 hours (15 to 38 hours)	39 hours or 1.5 days (29 - 51 h)
Initial Bacterial Count (Bacteremia)	33 cfu to >650,000 cfu/mL	600 cfu to >7,000,000 cfu/mL	10 cfu to >200,000 cfu/mL	3×10^6 to 9×10^8 cfu/mL (terminal)
Timing of Bacteremia	48 to 72 hours (100% + by Day2)	48 to 72 hours (50% + by Day 2)	66 hours (43 to 94 hours)	60 hours (48 to 72 hours)

Parameter	Battelle Study 617-G607610	Battelle Study 875-G607610	LLRI	USAMRIID
Radiographic abnormalities	n/a	n/a	5 out of 10 on Day 3	4 out of 4 on 80 to 83h post-exposure
Symptoms	Fever, loss of appetite, respiratory distress, bloody respiratory secretions, lethargy	Fever, hunched posture, respiratory distress, bloody respiratory secretions, lethargy	Fever, loss of appetite, diarrhea, lethargy	Fever, loss of appetite, respiratory distress, lethargy
Pathology	hemorrhagic pneumonia	hemorrhagic pneumonia	Fibrinosuppurative hemorrhagic pneumonia	Fibrinosuppurative hemorrhagic pneumonia

Source: Table 47 from Dr. Yasinskaya's review

Based on the findings from these four studies, and review of descriptions of pneumonic plague in humans from the published literature, the disease is sufficiently similar between humans and AGMs that the AGM model of pneumonic plague may be considered well-characterized for the purposes of predicting response in humans. Table 2 depicts the comparison between features of pneumonic plague in AGMs and humans.

Table 2 Comparison of Pneumonic Plague in Humans and the African Green Monkey Model of Pneumonic Plague

	Human	**African Green Monkey**
Time course of disease, days	2 to 9	2 to 9
Temperature	Elevated in ~100% of cases	Elevated in 100% of cases
***Y. pestis* present**	Positive in 100% of sputum	Positive in 100% of blood or lung/nasal fluids
Heart rate	Elevated	Elevated
Respiration rate	Elevated late in disease	Elevated late in disease
Chest radiographs	Pulmonary infiltrates, 90% bilateral	Pulmonary infiltrates, 80% bilateral
Pathology of lung	Consolidation Inflammatory infiltrates Hemorrhagic/frothy fluid Exudates and effusions Bronchopneumonia Bacilli	Bacteria Edema Hemorrhage Inflammatory infiltrates Bronchopneumonia Pleural fibrin

Source: Applicant's study report, Study FY07-070

As evidenced by the natural history studies, the AGM model of pneumonic plague is similar to human pneumonic plague with respect to the time course of disease, the time to onset of fever post-exposure, mortality, chest radiographic findings and pulmonary histopathology.

Since the AGM model of pneumonic plague was sufficiently well characterized, it was used for the pivotal efficacy study of levofloxacin, Study Number FY07-070.

The study was a randomized, investigator-blinded, treatment study of levofloxacin vs. placebo in AGMs exposed to aerosolized *Y. pestis*. The objective of the study was to determine if treatment with IV levofloxacin improved the survival rate among treated animals compared to those that received placebo.

Three cohorts of AGMs were studied using a total of 26 animals. Two animals were removed from the study; one animal due to health reasons immediately post-randomization (levofloxacin group) and one animal (also post-randomization from the levofloxacin group) due to a protocol deviation because the animal received levofloxacin treatment prior to the development of fever. A total of 24 animals, 12 males and 12 females remained in the study.

Each cohort of AGMs was challenged by head-only aerosol inhalation with a target dose of 100 $\pm$ 50 LD_{50} of *Y. pestis* strain CO92, which was a strain isolated from a fatal case of a patient with pneumonic plague. Based on the results of the natural history studies, established pneumonic plague was indicated by a mean body temperature of > 39ºC for at least one hour, which was the trigger to initiate levofloxacin or placebo infusion. Animals were administered the humanized dose of levofloxacin 8 mg/kg IV followed by 2 mg/kg 12 hours later or placebo infusion for 10 days. Infusions continued until the death of the animal or until 20 infusions had been delivered. Animals were monitored for up to 28 days post-challenge by twice daily observations and continuous monitoring of heart rate, respiration rate, and temperature via implanted telemeters.

As mentioned previously, the primary endpoint was the difference in 28-day survival of the levofloxacin-treated animals compared to the placebo-treated animals. The applicant analyzed 24 animals in their primary intent-to-treat (ITT) analysis. FDA reviewers conducted sensitivity analyses to evaluate the robustness of the findings from the primary analysis. These included analyzing cohorts 1 and 2 only, because the applicant added cohort 3 only after the results of the first two cohorts were known in order to obtain PK information; analyzing animals that received a challenge dose of > 20XLD_{50} because that was the dose associated with mortality in the natural history studies; analyzing only animals that were bacteremic; analyzing animals that had radiographic evidence of pneumonia; and analyzing animals that had a microbiologic response, i.e. no *Y. pestis* isolated from cultures at study termination on Day 28 or at the time of death/euthanasia. Table 3 below shows the results of these analyses.

Table 3 Survival Rates and Microbiological Response of the levofloxacin-treated compared to placebo-treated AGMs exposed to *Y. pestis* CO92

	Levofloxacin			**Placebo**			**95% CI**	**p-value**
	N	n	%	N	n	%		
Survival								
ITT	17	16	94	7	0	0	42.1, 98.6	<0.0001

Cohort 1 and 2	9	9	100	5	0	0	47.4, 100	0.0005
Challenge Dose	11	11	100	7	0	0	58.9, 100	<0.0001
Bacteremic	12	11	92	5	0	0	28.0, 99.8	0.001
Radiographic evidence	9	9	100	3	0	0	29.0, 100	0.005
Microbiologic response	17	14	83	7	0	0	29.0, 96.3	0.0003

Source: Table 33 from FDA Clinical Microbiology review by Simone Shurland, PhD

The results of the primary analysis and sensitivity analyses were all statistically very robust, with p-values ranging from <0.0001-0.005. This pivotal efficacy study provides strong evidence for the treatment of pneumonic and septicemic plague in AGMs with levofloxacin at a humanized dose for 10 days that achieves exposures similar to, but somewhat lower than, a human dose of 500 mg IV q d. This study is supported by efficacy in the rodent studies of plague, as well as from human studies in severe infections with Gram negative bacteria, particularly nosocomial pneumonia.

6.0 Summary of Clinical Safety

There is no new human safety data as no human clinical studies were conducted in support of this indication. However, the safety profile of levofloxacin is well established and has been evaluated in 7,537 subjects in 29 pooled phase 3 clinical trials. An estimated (b) (4) treatment courses were dispensed in 2010 and (b) (4) in 2009. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, constipation, and dizziness. The drug label includes boxed warnings for musculoskeletal events i.e. tendinitis, tendon rupture and exacerbation of muscle weakness in patients with myasthenia gravis. Other adverse reactions include hypersensitivity central nervous system disorders such as convulsions, psychoses, increased intracranial pressure/pseudotumor cerebri, peripheral neuropathy, QT interval prolongation, hepatitis, blood glucose disturbance, photosensitivity, and *Clostridium difficile* associated diarrhea. Other rare adverse reactions include severe dermatologic reactions such as toxic epidermal necrolysis and Steven Johnson syndrome, allergic pneumonitis, interstitial nephritis, severe, sometimes fatal hepatitis, and hematologic toxicities (agranulocytosis, thrombocytopenia). The safety information is described in the product labeling and in a Medication Guide.

There is safety information for 1,534 pediatric patients, ages 6 months to 16 years, who have been exposed to levofloxacin. Clinically significant adverse reactions included musculoskeletal disorders in 2-3.5%. Arthralgia in weight bearing joints was the most common adverse reaction in pediatric patients. Arthritis, tendinopathy, and gait abnormalities were also reported. These musculoskeletal disorders resolved in all patients without sequelae and 80% of them resolved within two months.

7.0 Summary of Other Regulatory Issues

These supplements were presented at a meeting of the Anti-infective Drugs Advisory Committee meeting on April 4, 2012. The committee voted unanimously that the AGM model of plague provided substantial evidence of the effectiveness of levofloxacin for the treatment of pneumonic plague. The committee members also had no recommendations for additional safety studies in humans and stated that adequate safety information is described in the levofloxacin U.S. Package Insert (USPI).

The Office of Scientific Investigations conducted audits of the sites where the levofloxacin efficacy study (Lovelace) and three of the natural history studies (Batelle and Lovelace) were conducted, as well as sites where pharmacokinetic studies of levofloxacin in AGM or methods validation procedures were conducted. 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. Specifically, a high performance liquid chromatography/triple quadrapole mass spectrometry (HPLC/MS/MS) assay that had been developed at (b) (4) for the determination of levofloxacin levels in AGM plasma was determined to be unsuitable because it performed poorly; results were uninterpretable, and not consistently within the validated range of the assay. That assay was abandoned and an HPLC/fluorescence detection (FLD) assay was developed and quantified by (b) (4) for use in Cohort 3 of the efficacy study.

At a meeting of the FDA pediatric review committee on March 14, 2012, the committee agreed with the Division's proposal for extrapolation from AGMs to pediatric patients aged 6 months or older and agreed that a waiver for patients younger than 6 months of age was appropriate. Safety and PK studies in this younger age group would be infeasible, as the occurrence of plague is extremely rare in all age groups.

The USPI and Medication Guide have been reviewed by colleagues in DDTCP and DMPP and their comments have been conveyed to the applicant. The Medication Guide will be revised to include information stating that the plague indication is supported by animal data only, as is required under the Animal Rule (21 CFR 314.000 Subpart I). The Animal Rule permits the Agency to require postmarketing restrictions as needed to ensure safe use, however since levofloxacin is an approved product that is used without restrictions on distribution or use for less serious indications, no such restrictions are necessary in this case. In order to meet an additional requirement of the Animal Rule, the

applicant will be required to conduct a postmarketing study, such as a field study, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

8.0 Regulatory Action

I concur with the findings and recommendations of the review team that the applicant has met the requirements of 21 CFR 314.000 Subpart I and demonstrated the efficacy of levofloxacin in the treatment of plague in a well-characterized animal model, the African Green Monkey. This efficacy study is supported by data on treatment of plague with levofloxacin in rodents, and by the approved indication for nosocomial pneumonia and other serious bacterial infections at a number of different body, which may be caused by related Gram-negative bacteria. The risk/benefit assessment is favorable as untreated pneumonic and septicemic plague is generally fatal, and a large survival benefit outweighs the known and labeled risks of levofloxacin. These supplements will be approved for the indication of plague, both treatment and prophylaxis, with the field study as a post-marketing requirement.

Katherine A. Laessig, MD

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KATHERINE A LAESSIG
04/27/2012