CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

Trade Name: **Levaquin**

Generic Name: **levofloxacin**

Sponsor: **Johnson & Johnson PRD**

Approval Date: **October 23, 2003**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	X
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634/S-028
NDA 20-635/S-027

Johnson & Johnson Pharmaceutical Research and Development
Attention: Robyn S. Keown, Sr. Regulatory Associate, Regulatory Affairs
920 Rte. 202 South, PO Box 300
Raritan, N J 08869-0602

Dear Ms. Keown:

Please refer to your supplemental new drug applications, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Date of Supplement	Date of Receipt	Name of Drug Product
20-634	S-028	December 20, 2002	December 23, 2002	Levaquin (levofloxacin) Tablets
20-635	S-027	December 23, 2002	December 23, 2002	Levaquin (levofloxacin) Injection and Levaquin (levofloxacin in 5% dextrose injection) Injection

We acknowledge receipt of your submissions dated:

April 4, 2003
April 24, 2003
June 6, 2003
August 19, 2003
October 16, 2003
October 21, 2003 (2)

These supplemental new drug applications provide for the use of Levaquin Tablets and Injection for Community Acquired Pneumonia (CAP) with a new dosing regimen of 750 mg, once daily for 5 days.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, submitted on October 21, 2003).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA.* Alternatively, you may submit 20 paper copies

of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-634/S-028, NDA 20-635/S-027." Approval of these submissions by the FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment dated October 21, 2003, submitted in follow-up to our teleconference of October 21, 2003. During that teleconference, we discussed the need to investigate the efficacy observed in patients with renal impairment who received 750 mg every 48 hours. This commitment is listed below:

1. Conduct a pharmacokinetic study utilizing the LEVAQUIN 750 mg dose in otherwise healthy, renally-impaired patients to characterize drug exposure following the dosage adjustments recommended in the product label.

Protocol Submission:	Within 6-9 months of the date of this letter
Study Start:	Within 10-12 months of the date of this letter
Final Report Submission:	Within 24-26 months of the date of this letter

Submit clinical protocols to your INDs for these products. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual reports to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence.**"

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, if you do not conduct pediatric clinical trials as outlined in your Written Request, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. We acknowledge your Written Request, dated December 20, 2001, as part of which you will conduct a clinical trial in pediatric patients with community acquired pneumonia.

Please submit three copies of the introductory promotional materials that you propose to use for this new dosing regimen for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure (labeling)

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

/s/

Renata Albrecht

10/23/03 07:06:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

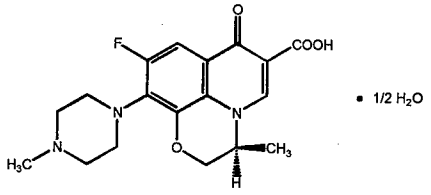
20-634 / S-028
20-635 / S-027

LABELING

LEVAQUIN® (levofloxacin) Tablets
LEVAQUIN® (levofloxacin) Injection
LEVAQUIN® (levofloxacin in 5% dextrose) Injection

DESCRIPTION

LEVAQUIN® (levofloxacin) is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

The chemical structure is: 

Its empirical formula is $C_{18}H_{20}FN_3O_4 \bullet ½ H_2O$ and its molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble to freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered *freely soluble* in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: $Al^{+3}>Cu^{+2}>Zn^{+2}>Mg^{+2}>Ca^{+2}$.

LEVAQUIN Tablets are available as film-coated tablets and contain the following inactive ingredients:

250 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.

500 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.

750 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline

cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80.

LEVAQUIN Injection in Single-Use Vials is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. LEVAQUIN Injection in Premix Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. The appearance of LEVAQUIN Injection may range from a clear yellow to a greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN Injection in Single-Use Vials contains levofloxacin in Water for Injection. LEVAQUIN Injection in Premix Flexible Containers is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D_5W). Solutions of hydrochloric acid and sodium hydroxide may have been added to adjust the pH.

The flexible container is fabricated from a specially formulated non-plasticized, thermoplastic copolyester (CR3). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers.

CLINICAL PHARMACOLOGY

The mean ±SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral (p.o.) or intravenous (i.v.) doses of levofloxacin are summarized in Table 1.

Absorption

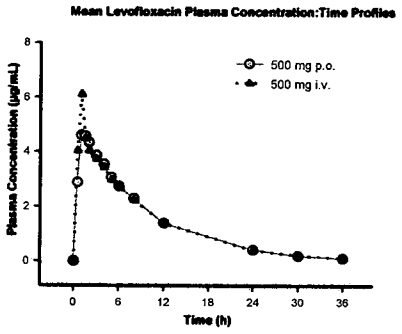
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean ±SD peak plasma concentration attained was 6.2 ±1.0 µg/mL after a 500 mg dose infused over 60 minutes and 11.5 ±4.0 µg/mL after a 750 mg dose infused over 90 minutes.

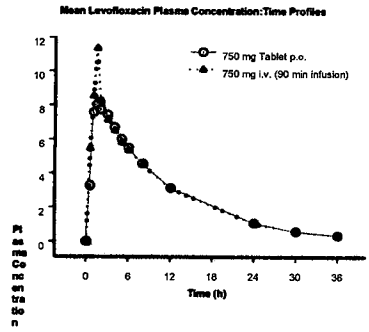
Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2 µg/mL after the 500 mg doses, and 8.6 ±1.9 and 1.1 ±0.4 µg/mL after the 750 mg

doses, respectively. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily i.v. regimens were approximately 6.4 ±0.8 and 0.6 ±0.2 µg/mL after the 500 mg doses, and 12.1 ±4.1 and 1.3 ±0.71 µg/mL after the 750 mg doses, respectively.

Oral administration of a 500-mg LEVAQUIN tablet with food slightly prolongs the time to peak concentration by approximately 1 hour and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin tablets can be administered without regard to food.

The plasma concentration profile of levofloxacin after i.v. administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and i.v. routes of administration can be considered interchangeable. (See following chart.)





Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg levofloxacin, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5- fold higher than plasma concentrations and ranged from approximately 2.4 to

11.3 μg/g over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 μg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Special Populations

Geriatric: There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 - 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment

based on age alone is not necessary.

Pediatric: The pharmacokinetics of levofloxacin in pediatric subjects have not been studied.

Gender: There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race: The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 non-white. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal insufficiency: Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**.)

Hepatic insufficiency: Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial infection: The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug-drug interactions: The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, and antacids has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)

Table 1. Mean ±SD Levofloxacin PK Parameters

Regimen	C_{max} (µg/mL)	T_{max} (h)	AUC (µgh/mL)	CL/F[1] (mL/min)	Vd/F[2] (L)	$t_{1/2}$ (h)	CL_R (mL/min)
Single dose							
250 mg p.o.[3]	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg p.o.[3]*	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg i.v.[3]	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg p.o.[5*]	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg i.v.[5]	11.5 ±4.0[4]	ND	110 ±40	126 ±39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg q24h p.o.[3]	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg q24h i.v.[3]	6.4 ± 0.8	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg q24h i.v., patients with bacterial infection[6]	8.7± 4.0[7]	ND	72.5 ± 51.2[7]	154 ± 72	111 ± 58	ND	ND
750 mg q24h p.o.[5]	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg q24h i.v.[5]	12.1 ± 4.1[4]	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg p.o. single dose, effects of gender and age:							
male[8]	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female[9]	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
young[10]	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
Elderly[11]	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg p.o. single dose, patients with renal insufficiency:							
CL_{CR} 50-80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
CL_{CR} 20-49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CL_{CR} <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND

[1] clearance/bioavailability

[2] volume of distribution/bioavailability

[3] healthy males 18-53 years of age

[4] 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

[5] healthy male and female subjects 18-54 years of age

[6] 500 mg q48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin

[7] dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling

[8] healthy males 22-75 years of age

[9] healthy females 18-80 years of age

[10] young healthy male and female subjects 18-36 years of age

[11] healthy elderly male and female subjects 66-80 years of age

*Absolute bioavailability; $F = 0.99 \pm 0.08$ from a 500-mg tablet and $F = 0.99 \pm 0.06$ from a 750-mg tablet ; ND = not determined.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicilllin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including penicillin-resistant strains*)

Streptococcus pyogenes

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of ≥2 μg/mL

Aerobic gram-negative microorganisms

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

The following in vitro data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 μg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus

Streptococcus (Group C/F)

Streptococcus (Group G)

Streptococcus agalactiae

Streptococcus milleri

Viridans group *streptococci*

Aerobic gram-negative microorganisms

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter (diversus) koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea (Enterobacter) agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Anaerobic gram-positive microorganisms

Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa:*

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[a]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *S. pneumoniae*:[b]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

Microorganism		MIC (µg/mL)
Enterococcus faecalis	**ATCC 29212**	**0.25 – 2**
Escherichia coli	ATCC 25922	0.008 - 0.06
Escherichia coli	ATCC 35218	0.015 - 0.06
Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Pseudomonas aeruginosa	**ATCC 27853**	**0.5 – 4**

Staphylococcus aureus	ATCC 29213	0.06 - 0.5
Streptococcus pneumoniae	ATCC 49619[d]	**0.5 – 2**

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg levofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa:*

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[e]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp. including *S. pneumoniae*:[f]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus* spp. including *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29 - 37
Haemophilus influenzae	ATCC 49247[g]	32 - 40
Pseudomonas aeruginosa	ATCC 27853	19 - 26
Staphylococcus aureus	ATCC 25923	25 - 30
Streptococcus pneumoniae	ATCC 49619[h]	20 - 25

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).[2]

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

LEVAQUIN Tablets/Injection are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. LEVAQUIN Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute maxillary sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis.*

Acute bacterial exacerbation of chronic bronchitis due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae*, or *Moraxella catarrhalis.*

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,* or *Streptococcus pneumoniae.* Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended. (See **CLINICAL STUDIES.)**

Community-acquired pneumonia due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥2 µg/mL), *Haemophilus*

influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila, or *Mycoplasma pneumoniae.* (See **CLINICAL STUDIES.**)

Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes, or Proteus mirabilis.*

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus* or *Streptococcus pyogenes.*

Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or *Staphylococcus epidermidis.*

Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa.*

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli.*

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus.*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

WARNINGS

THE SAFETY AND EFFICACY OF LEVOFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy**, and **Nursing Mothers** subsections.)

In immature rats and dogs, the oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS.)**

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of

multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS.**)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS.**)

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

PRECAUTIONS

General

Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS

INFUSION OVER A PERIOD OF 60 OR 90 MINUTES DEPENDING ON THE DOSAGE. (See **DOSAGE AND ADMINISTRATION.**)

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance **<50** mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **WARNINGS** and **Drug Interactions.**)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately. (See **Drug Interactions** and **ADVERSE REACTIONS.**)

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk

factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided.

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Information for Patients

Patients should be advised:

- to drink fluids liberally;
- that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx®, (didanosine), chewable/buffered tablets or the pediatric powder for oral solution should be taken at least two hours before or two hours after oral levofloxacin administration. (See **Drug Interactions**);
- that oral levofloxacin can be taken without regard to meals;
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**);
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS**);
- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs;
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a

physician. (See **PRECAUTIONS: General** and **Drug Interactions.**);

- that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin.
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN Tablets: While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of LEVAQUIN Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx® (didanosine), chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

LEVAQUIN Injection: There are no data concerning an interaction of **intravenous** quinolones with **oral** antacids, sucralfate, multivitamins, Videx®, (didanosine), or metal cations. However, no quinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND ADMINISTRATION.**)

Theophylline: No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels. (See **WARNINGS** and **PRECAUTIONS: General.**)

Warfarin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving

healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Cyclosporine: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine: No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and CL_R were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See **WARNINGS** and **PRECAUTIONS: General.**)

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 μg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 μg/g at Cmax.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS.**)

Geriatric Use

In phase 3 clinical trials, 1,190 levofloxacin-treated patients (25%) were ≥65 years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.2%. Among patients receiving levofloxacin therapy, 4.3% discontinued levofloxacin therapy due to adverse experiences. The overall incidence, type and distribution of adverse events was similar in patients receiving levofloxacin doses of 750 mg once daily compared to patients receiving doses from 250 mg once daily to 500 mg twice daily.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:

Nausea 1.2%, diarrhea 1.0%, vaginitis 0.6%, insomnia 0.4%, abdominal pain 0.4%, flatulence 0.3%, pruritus 0.3%, dizziness 0.3%, rash 0.3%, dyspepsia 0.2%, genital moniliasis 0.2%, moniliasis 0.2%, taste perversion 0.2%, vomiting 0.2%, injection site pain 0.2%, injection site reaction 0.2%, injection site inflammation 0.1%, constipation 0.1%, fungal infection 0.1%,

genital pruritis 0.1%, headache 0.1%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%, anorexia 0.1%, somnolence 0.1%, agitation 0.1%, rash maculo-papular 0.1%, tremor 0.1%, condition aggravated 0.1%, allergic reaction 0.1%.

In clinical trials, the following events occurred in >3% of patients, regardless of drug relationship:

nausea 7.1%, headache 6.2%, diarrhea 5.5%, insomnia 5.1%, constipation 3.5%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

abdominal pain 2.7%, dizziness 2.5%, vomiting 2.5%, dyspepsia 2.3%, vaginitis 1.7%, rash 1.6%, chest pain 1.4%, pruritus 1.3%, sinusitis 1.3%, dyspnea 1.4%, fatigue 1.4%, flatulence 1.2%, pain 1.6%, back pain 1.2%, rhinitis 1.2%, anxiety 1.2%, pharyngitis 1.2%

In clinical trials, the following events, of potential medical importance, occurred at a rate of 0.1% to 0.9%, regardless of drug relationship

Body as a **Whole** – General Disorders:	Ascites, allergic reaction, asthenia, drug level increase, edema, enlarged abdomen, fever, headache, hot flashes, influenza-like symptoms, leg pain, malaise, rigors, substernal chest pain, syncope, multiple organ failure,changed temperature sensation, withdrawal syndrome
Cardiovascular Disorders, General:	Cardiac failure, hypertension, hypertension aggravated, hypotension, postural hypotension
Central and Peripheral Nervous System Disorders:	Convulsions (seizures), dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, migraine, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo, encephalopathy, abnormal gait, leg cramps, intracranial hypertension, ataxia
Gastro-Intestinal System Disorders:	Dry mouth, dysphagia, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, G.I. hemorrhage, glossititis, hemorrhoids, intestinal obstruction, pancreatitis, tongue edema, melena, stomatitis
Hearing and Vestibular Disorders:	Earache, tinnitus
Heart Rate and Rhythm Disorders:	Arrhythmia, arrhythmia ventricular, atrial fibrillation, bradycardia, cardiac arrest, ventricular fibrillation, heart block, palpitation, supraventricular tachycardia, ventricular tachycardia, tachycardia
Liver and Biliary System Disorders:	Abnormal hepatic function, cholecystitis, cholelithiasis, elevated bilirubin, hepatic enzymes increased, hepatic failure, jaundice

Disorders:	
Metabolic and Nutritional Disorders:	Hypomagnesemia, thirst, dehydration, electrolyte abnormality, fluid overload, gout, hyperglycemia, hyperkalemia, hypernatremia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, nonprotein nitrogen increase, weight decrease
Musculo-Skeletal System Disorders:	Arthralgia, arthritis, arthrosis, myalgia, osteomyelitis, skeletal pain, synovitis, tendonitis, tendon disorder
Myo, Endo, Pericardial and Valve Disorders:	Angina pectoris, endocarditis, myocardial infarction
Neoplasms:	Carcinoma, thrombocythemia
Other Special Senses Disorders:	Parosmia, taste perversion
Platelet, Bleeding and Clotting Disorders:	Hematoma, epistaxis, prothrombin decreased, pulmonary embolism, purpura, thrombocytopenia
Psychiatric Disorders:	Abnormal dreaming, agitation, anorexia, confusion, depression, hallucination, impotence, nervousness, paroniria, sleep disorder, somnolence
Red Blood Cell Disorders:	Anemia
Reproductive Disorders:	Dysmenorrhea, leukorrhea
Resistance Mechanism Disorders:	Abscess, bacterial infection, fungal infection, herpes simplex, moniliasis, otitis media, sepsis, viral infection
Respiratory System Disorders:	Airways obstruction, aspiration, asthma, bronchitis, bronchospasm, chronic obstructive airway disease, coughing, hemoptysis, epistaxis, hypoxia, laryngitis, pharyngitis, pleural effusion, pleurisy, pneumonitis, pneumonia, pneumothorax, pulmonary collapse, pulmonary edema, respiratory depression, respiratory insufficiency, upper respiratory tract infection
Skin and Appendages Disorders:	Alopecia, bullous eruption, dry skin, eczema, genital pruritus, increased sweating, rash, skin exfoliation, skin ulceration, urticaria
Urinary System Disorders:	Abnormal renal function, acute renal failure, dysuria, hematuria, oliguria, urinary incontinence, urinary retention, urinary tract infection,
Vascular (Extracardiac) Disorders:	Flushing, gangrene, phlebitis, purpura, thrombophlebitis (deep)
Vision Disorders:	Abnormal vision, eye pain, conjunctivitis
White Cell and RES Disorders:	Agranulocytosis, granulocytopenia, leukocytosis, lymphadenopathy

RES Disorders:

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

Crystalluria and cylindruria have been reported with other quinolones.

The following markedly abnormal laboratory values appeared in >2% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Blood Chemistry: decreased glucose (2.2%)

Hematology: decreased lymphocytes (2.2%)

Post-Marketing Adverse Reactions

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio (INR)/prothrombin time, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, vasodilation.

OVERDOSAGE

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

LEVAQUIN Injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED. Levofloxacin Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. (See **PRECAUTIONS.**)

Single-use vials require dilution prior to administration. (See **PREPARATION FOR ADMINISTRATION.**)

The usual dose of LEVAQUIN Tablets or Injection is 250 mg or 500 mg administered orally or by slow infusion over 60 minutes every 24 hours or 750 mg administered orally or by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance > 80 mL/min). For patients with altered renal function see the **Patients with Impaired Renal Function** subsection. Oral doses should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx®, (didanosine), chewable/buffered tablets or the pediatric powder for oral solution.

Patients with Normal Renal Function

Infection*	Unit Dose	Freq.	Duration**	Daily Dose
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Comm. Acquired Pneumonia	750 mg***	q24h	5 days	750 mg
Nosocomial Pneumonia	750 mg	q24h	7-14 days	750 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 mg
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Acute Maxillary Sinusitis	500 mg	q24h	10-14 days	500 mg
Uncomplicated SSSI	500 mg	q24h	7-10 days	500 mg
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg

* **DUE TO THE DESIGNATED PATHOGENS (See INDICATIONS AND USAGE.)**

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

*** Efficacy of this alternative regimen has only been documented for infections caused by penicillin-susceptible *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae* and

Chlamydia pneumoniae.

Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis / Comm. Acquired Pneumonia / Acute Maxillary Sinusitis / Uncomplicated SSSI/Chronic Bacterial Prostatitis		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI/Nosocomial Pneumonia/ Comm. Acquired Pneumonia		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI / Acute Pyelonephritis		
$CL_{CR} \geq 20$ mL/min	No dosage adjustment required	
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{CR}=creatinine clearances
CAPD=chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine Clearance (mL/min) =

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

Preparation of Levofloxacin Injection for Administration

LEVAQUIN Injection in Single-Use Vials: LEVAQUIN Injection is supplied in single-use

vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of levofloxacin/mL. **THESE LEVAQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION.** (See **COMPATIBLE INTRAVENOUS SOLUTIONS.**) The concentration of the resulting diluted solution should be 5 mg/mL prior to administration.

This intravenous drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. **Since the vials are for single-use only, any unused portion remaining in the vial should be discarded. When used to prepare two 250 mg doses from the 20 mL vial containing 500 mg of levofloxacin, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use.** (See **Stability of LEVAQUIN Injection Following Dilution.**)

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Prepare the desired dosage of levofloxacin according to the following chart:

Desired Dosage Strength	From Appropriate Vial, Withdraw Volume	Volume of Diluent	Infusion Time
250 mg	10 mL (20 mL Vial)	40 mL	60 min
500 mg	20 mL (20 mL Vial)	80 mL	60 min
750 mg	30 mL (30 mL Vial)	120 mL	90 min

For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL), withdraw 20 mL and dilute with a compatible intravenous solution to a total volume of 100 mL.

Compatible Intravenous Solutions: Any of the following intravenous solutions may be used to prepare a 5 mg/mL levofloxacin solution with the approximate pH values:

Intravenous Fluids	Final pH of LEVAQUIN Solution
0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte® 56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

LEVAQUIN Injection Premix in Single-Use Flexible Containers: LEVAQUIN Injection is also supplied in flexible containers containing a premixed, ready-to-use levofloxacin solution in D_5W for single-use. The fill volume is either 50 or 100 mL for the 100 mL flexible container or 150 mL for the 150 mL container. **NO FURTHER DILUTION OF THESE PREPARATIONS ARE NECESSARY. Consequently each 50 mL, 100 mL, and 150 mL premix flexible container already contains a dilute solution with the equivalent of 250 mg, 500 mg, and 750 mg of levofloxacin, respectively (5 mg/mL) in 5% Dextrose (D_5W).**

This parenteral drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since the premix flexible containers are for single-use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in flexible containers or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the Use of LEVAQUIN Injection Premix in Flexible Containers

To open:

1. Tear outer wrap at the notch and remove solution container.

2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.

3. Do not use if the solution is cloudy or a precipitate is present.

4. Use sterile equipment.

5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Close flow control clamp of administration set.

2. Remove cover from port at bottom of container.

3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. **NOTE: See full directions on administration set carton.**

4. Suspend container from hanger.

5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of LEVAQUIN Injection in Premix Flexible Containers.

6. Open flow control clamp to expel air from set. Close clamp.

7. Regulate rate of administration with flow control clamp.

Stability of LEVAQUIN Injection as Supplied

When stored under recommended conditions, LEVAQUIN Injection, as supplied in 20 mL and 30 mL vials, or 100 mL and 150 mL flexible containers, is stable through the expiration date printed on the label.

Stability of LEVAQUIN Injection Following Dilution

LEVAQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 72 hours when stored at or below 25°C (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass bottles or plastic intravenous containers are stable for 6 months when stored at -20°C (-4°F). **THAW FROZEN SOLUTIONS AT ROOM TEMPERATURE 25°C (77°F) OR IN A REFRIGERATOR 8°C (46°F). DO NOT FORCE THAW BY MICROWAVE IRRADIATION OR WATER BATH IMMERSION. DO NOT REFREEZE AFTER INITIAL THAWING.**

HOW SUPPLIED

LEVAQUIN Tablets

LEVAQUIN (levofloxacin) Tablets are supplied as 250, 500, and 750 mg modified rectangular,

film-coated tablets. LEVAQUIN Tablets are packaged in bottles and in unit-dose blister strips in the following configurations:

250 mg tablets: color: terra cotta pink

debossing: "LEVAQUIN" on side 1 and "250" on side 2

bottles of 50 (NDC 0045-1520-50)

unit-dose/100 tablets (NDC 0045-1520-10)

500 mg tablets: color: peach

debossing: "LEVAQUIN" on side 1 and "500" on side 2

bottles of 50 (NDC 0045-1525-50)

unit-dose/100 tablets (NDC 0045-1525-10)

750 mg tablets: color: white

debossing: "LEVAQUIN" on side 1 and "750" on side 2

bottles of 50 (NDC 0045-1530-50)

unit-dose/100 tablets (NDC 0045-1530-10)

LEVA-pak unit-dose/5 tablets (NDC 0045-1530-05)

LEVAQUIN Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

LEVAQUIN Tablets are manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

LEVAQUIN Injection

Single-Use Vials: LEVAQUIN (levofloxacin) Injection is supplied in single-use vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL vials.

25 mg/mL, 20 mL vials (NDC 0045-0069-51)

25 mg/mL, 30 mL vials (NDC 0045-0065-55)

LEVAQUIN Injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

LEVAQUIN Injection in Single-Use Vials is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by OMJ Pharmaceuticals, Inc., San German, Puerto

Rico, 00683.

Premix in Flexible Containers: LEVAQUIN (levofloxacin in 5% dextrose) Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D_5W).

5 mg/mL (250 mg), 50 mL flexible container (NDC 0045-0067-01)

5 mg/mL (500 mg), 100 mL flexible container (NDC 0045-0068-01)

5 mg/mL (750 mg), 150 mL flexible container (NDC 0045-0066-01)

LEVAQUIN Injection Premix in Flexible Containers should be stored at or below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light.

LEVAQUIN Injection Premix in Flexible Containers is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by ABBOTT Laboratories, North Chicago, IL 60064.

CLINICAL STUDIES

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7-15 days to intravenous imipenem/cilastatin (500-1000 mg q6-8 hours daily) followed by oral ciprofloxacin (750 mg q12 hours daily) for a total of 7-15 days. Levofloxacin-treated patients received an average of 7 days of intravenous therapy (range: 1-16 days); comparator-treated patients received an average of 8 days intravenous therapy (range: 1-19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the levofloxacin arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the levofloxacin arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the levofloxacin arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection.

Clinical success rates in clinically and microbiologically evaluable patients at the posttherapy visit (primary study endpoint assessed on day 3-15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen were as follows:

Pathogen	Levofloxacin No. (%) of Patients N	Microbiologic / Clinical Outcomes	Imipenem/Cilastatin No. (%) of Patients N	Microbiologic / Clinical Outcomes
MSSA[a]	21	14 (66.7) / 13 (61.9)	19	13 (68.4) / 15 (78.9)
P. aeruginosa[b]	17	10 (58.8) / 11 (64.7)	17	5 (29.4) / 7 (41.2)
S. marcescens	11	9 (81.8) / 7 (63.6)	7	2 (28.6) / 3 (42.9)
E. coli	12	10 (83.3) / 7 (58.3)	11	7 (63.6) / 8 (72.7)
K. pneumoniae[c]	11	9 (81.8) / 5 (45.5)	7	6 (85.7) / 3 (42.9)
H. influenzae	16	13 (81.3) /10 (62.5)	15	14 (93.3) / 11 (73.3)
S. pneumoniae	4	3 (75.0) / 3 (75.0)	7	5 (71.4) / 4 (57.1)

[a] Methicillin-susceptible *S. aureus.*

[b] See above text for use of combination therapy.

[c] The observed differences in rates for the clinical and microbiological outcome may reflect other factors that were not accounted for in the study.

Community-Acquired Bacterial Pneumonia

7 to 14 Day Treatment Regimen

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in two pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies were as follows:

Pathogen	No. Pathogens	Microbiologic Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin-resistant strains (MIC value for penicillin —2 µg/mL). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double-blind study, two open label randomized studies, and three open label non-comparative studies. The total number of clinically evaluable patients with *S.pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with *S. pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator-treated

patients with *S. pneumoniae* was 39/41 (95%).

Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* (MIC value for penicillin —2 μg/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having severe disease. Of the 4 comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator-treated patients achieved clinical success. All three of the comparator-treated patients were bacteremic and had disease classified as severe.

Community-Acquired Bacterial Pneumonia

5-Day Treatment Regimen

To evaluate the safety and efficacy of higher dose and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg, i.v. or p.o., q.d. for five days or levofloxacin 500 mg i.v. or p.o., q.d. for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in the levofloxacin 750mg group and 91.1% in the levofloxacin 500 mg group. The 95% CI for the difference of response rates (levofloxacin 750 minus levofloxacin 500) was [-5.9, 5.4]. In the clinically evaluable population (31-38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the levofloxacin 750 mg group and 2 out of 147 patients in the levofloxacin 500 mg group. Given the small numbers observed, the significance of this finding can not be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in the table below.

	Eradication rate
Penicillin susceptible *S. pneumoniae*	19/20
Haemophilus influenzae	12/12
Haemophilus parainfluenzae	10/10
Mycoplasma pneumoniae	26/27
Chlamydia pneumoniae	13/15

Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to receive either levofloxacin 750 mg QD (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the levofloxacin and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the levofloxacin treated patients and 44% of the comparator treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2-5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral levofloxacin 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5-18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented below:

	Levofloxacin (N=136)		Ciprofloxacin (N=125)	
Pathogen	N	Eradication	N	Eradication
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	44	33 (75.0%)
**S. epidermidis*	11	9 (81.8%)	14	11 (78.6%)

*Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5-18 days after completion of therapy were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24-45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin minus ciprofloxacin).

ANIMAL PHARMACOLOGY

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS.**) In immature dogs (4 - 5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

In vitro and in vivo studies in animals indicate that levofloxacin is neither an enzyme inducer or inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests Eighth Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

Patient Information About:
LEVAQUIN®
(levofloxacin) Tablets
250 mg Tablets, 500 mg Tablets, and 750 mg Tablets

This leaflet contains important information about LEVAQUIN® (levofloxacin), and should be read completely before you begin treatment. This leaflet does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This leaflet does not list all benefits and risks of LEVAQUIN® . The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about LEVAQUIN® talk to your health care professional. Only your health care professional can determine if LEVAQUIN® is right for you.

What is LEVAQUIN®?

LEVAQUIN® is a quinolone antibiotic used to treat lung, sinus, skin, and urinary tract infections caused by certain germs called bacteria. LEVAQUIN® kills many of the types of bacteria that can infect the lungs, sinuses, skin, and urinary tract and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). LEVAQUIN®, like other antibiotics, does not kill viruses.

You should contact your health care professional if you think that your condition is not improving while taking LEVAQUIN®. LEVAQUIN® Tablets are terra cotta pink for the 250 mg tablet, peach colored for the 500 mg tablet, or white for the 750 mg tablet.

How and when should I take LEVAQUIN®?

LEVAQUIN® should be taken once a day for 3, 5, 7, 10, 14 or 28 days depending on your prescription. It should be swallowed and may be taken with or without food. Try to take the tablet at the same time each day and drink fluids liberally.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of LEVAQUIN® even if you missed a dose by mistake. You should not take a double dose.

Who should not take LEVAQUIN®?

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

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

LEVAQUIN® is not recommended for children.

What are possible side effects of LEVAQUIN®?

LEVAQUIN® is generally well tolerated. The most common side effects caused by LEVAQUIN®, which are usually mild, include nausea, diarrhea, itching, abdominal pain, dizziness, flatulence, rash and vaginitis in women.

You should be careful about driving or operating machinery until you are sure LEVAQUIN® is not causing dizziness.

Allergic reactions have been reported in patients receiving quinolones including LEVAQUIN®, even after just one dose. If you develop hives, skin rash or other symptoms of an allergic reaction, you should stop taking this medication and call your health care professional.

Ruptures of shoulder, hand, or Achilles tendons have been reported in patients receiving quinolones, including LEVAQUIN®. If you develop pain, swelling, or rupture of a tendon you should stop taking LEVAQUIN® and contact your health care professional.

Some quinolone antibiotics have been associated with the development of phototoxicity **("sunburns" and "blistering sunburns") following** exposure to sunlight or other sources of ultraviolet light such as artificial ultraviolet light used in tanning salons. LEVAQUIN® has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking LEVAQUIN®.

If you have diabetes and you develop a hypoglycemic reaction while on LEVAQUIN®, you should stop taking LEVAQUIN® and call your health care professional.

Convulsions have been reported in patients receiving quinolone antibiotics including LEVAQUIN®. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions.

Quinolones, including LEVAQUIN®, may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely, suicidal thoughts or acts.

If you notice any side effects not mentioned in this leaflet or you have concerns about the side effects you are experiencing, please inform your health care professional.

For more complete information regarding levofloxacin, please refer to the full prescribing information, which may be obtained from your health care professional, pharmacist, or the Physicians Desk Reference (PDR).

What about other medicines I am taking?

Taking warfarin (Coumadin®) and LEVAQUIN® together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your health care professional.

Many antacids and multivitamins may interfere with the absorption of LEVAQUIN® and may prevent it from working properly. You should take LEVAQUIN® either 2 hours before or 2 hours after taking these products.

It is important to let your health care professional know all of the medicines you are using.

Other information

Take your dose of LEVAQUIN® once a day.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

[ADD LOGO]
OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey, USA 08869

U.S. Patent No. 4,382,892 and U.S. Patent No. 5,053,407.

Revised October 2003
[ADD OMP AND ABBOTT CODES]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

MEDICAL REVIEW(S)

Medical Officer Review

Levofloxacin 750mg QD x 5 days for the treatment of Community Acquired Pneumonia

NDA number:	20-635/S027 and 20-634/S028
Submission date:	December 20th, 2002
Review complete:	October 22nd, 2003
Applicant:	Johnson and Johnson 920 US Highway 202 PO box 300 Raritan NJ 08869
Drug:	Levofloxacin (Levaquin®)
Therapeutic category:	Fluoroquinolone antimicrobial
Dosage form:	Tablet and intravenous solution
Route of administration:	Oral and intravenous

Primary reviewers (clinical):	Leonard Sacks Vicki Moncada
Medical team leader:	Rigoberto Roca
Project manager:	Susan Peacock

Table of contents

Executive Summary 1
Recommendations 1
Summary of clinical findings 1
Clinical review 4
Introduction and background 4
Proposed Labeling 4
State of Armamentarium for Indication(s) 4
Important Milestones in Product Development 6
Other Relevant Information 7
Important Issues with Pharmacologically Related Agents 7
Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and /or Other Consultant Reviews 7
Description of clinical data and sources: 9
Clinical review methods: 10
Integrated Review of Efficacy 11
Study Quality 11
Efficacy 11
Clinical cure rates, clinical improvement rates, clinical relapse rates 12
Subgroups 12
Conclusions 14
Integrated Review of Safety 15
Brief Statement of Conclusions 15
Description of Patient Exposure 16
Demographics 16
All Adverse Events 17
Drug Related Adverse Events: 18
Severe Adverse Events 19
Serious Adverse Events 19
Deaths 20
AEs leading to discontinuing study drug 21
QT Prolongation 21
Clinical Laboratory Evaluation 21
Conclusions Regarding Safety Data 22
Conclusions and Recommendations 23
Appendices 25
Appendix 1: Detailed efficacy review of individual trials 25
CAPS 150 25
CAPS 171 48
Appendix 2 57
CAPSS-150: Incidence of Adverse Events, by Body System 57
Appendix 3 58
CAPSS-171: Incidence of Adverse Events, by Body System 58
Appendix 4 59
CAPSS-150: Summary of Subjects who Died 59
Appendix 5 60
CAPSS-171: Summary of Subjects who Died 60
Appendix 6 61
CAPSS-150: Incidence of Adverse Events Resulting in Discontinuation 61
Appendix 7 62
CAPSS-171: Discontinuation fro Therapy due to Adverse Events 62
Appendix 8 63
CAPSS-150: Incidence of Treatment-emergent Markedly Abnormal Laboratory Values 63

Appendix 9 64
CAPSS-150: Subjects with Treatment-emergent Markedly Abnormal Laboratory Values 64
Appendix 10 65
CAPSS-171: Incidence of Treatment-emergent Markedly Abnormal Laboratory Values 65
Appendix 11 66
CAPSS-171: Subjects with Treatment-emergent Markedly Abnormal Laboratory Values 66

Executive Summary

Recommendations

Recommendations on approvability:
The medical officers recommends approval of the application. This is based on a single pivotal study demonstrating clinical equivalence between the investigational and the approved treatment regimens using levofloxacin for the treatment of Community Acquired Pneumonia (CAP).

Qualifications:

a) Relapse rates: The equivalence was demonstrated using a test of cure visit, 17-21 days after enrollment. Examination of outcome at a later time point 31-38 days post enrolment showed a trend to higher relapse rates in the 5-day treatment arm than the 10-day treatment arm (5% versus 1%). "Superinfections" with *S pneumoniae* after completion of treatment were also more common in the 5-day treatment arm than the 10-day treatment arm. It is possible that some of these superinfections may represent relapses, where the baseline pathogen was not identified. The reviewer recommends labeling to reflect the possibility of higher relapse rates with the short course regimen.

b) The organisms:
The microbiological efficacy was only adequately characterized for *S pneumoniae, H influenzae, H parainfluenzae, M pneumoniae,* and *C pneumoniae*. The short course regimen was not characterized for *S* [redacted] cases

Recommendations on post-marketing studies/risk management
In view of the high failure rates in patients with dosage adjustments due to renal dysfunction, the reviewer recommends a Phase 4 study to investigate the reason for the lower efficacy observed in patients with renal impairment and who had dose modifications performed. This may be initiated with further characterization the pharmacokinetics of levofloxacin in patients with a creatinine clearance below 50mg/min.

Summary of clinical findings

Brief overview of clinical program:
The aim of the program was to demonstrate comparative safety and efficacy using levofloxacin 750mg QD for 5 days, with the approved regimen of levofloxacin 500mg QD for 10 days in the treatment of community acquired pneumonia

The determination of efficacy was based on 1 blinded randomized comparative trial (CAPS150, 530 participants enrolled) and a second supportive non-comparative trial (CAPS 171, 124 participants enrolled). Both studies included adults (either hospitalized or outpatients) with Fine scores <130.
The primary endpoint was clinical success (cure or improvement) as determined by the investigator, 17-21 days after enrollment in the comparative study, and 12-16 days after enrollment in the uncontrolled study. Safety data was included from a study of febrile neutropenia where the same dose regimen was employed.

Efficacy:

CAPS 150 (comparative study)

Treatment arms: Levofloxacin (oral or intravenous) 750mg QD for 5 days
Levofloxacin (oral or intravenous) 500mg QD for 10 days

Patients in the 2 arms of the comparative study were balanced demographically, ethnically diverse, and included ~40% females. Individuals with creatinine clearance <50ml/min were excluded.

The reviewer regarded 115 of the enrolled patients as clinically unevaluable, mostly because of normal temperatures and white blood counts at entry.

CAPS 171 (non-comparative study)

Single treatment arm: Levofloxacin (oral or intravenous) 750mg QD for 5 days

Patients in this study were older, sicker (according to Fine score) and included 17 clinically evaluable patients with creatinine clearance <50ml/min for whom dosage adjustments were made.

a) Clinical efficacy:
A summary of the clinical efficacy in both studies is given below.

Table a: Clinical success rates

	CAPS 171[1]	CAPS 150[2]	
		5 day	10 day
Clinical success	59/74 (79.7%)	146/159 (92%)	141/154 (92%)

[1] test of cure 12-16 days post initiation of therapy
[2] test of cure 17-21 days post initiation of therapy

Clinical equivalence was demonstrated for the two treatment regimens in CAPS 150 [95% confidence interval (10- day minus 5-day) = -6.4% to 5.9%]

Table b: clinical efficacy (clinically evaluable population)

	CAPS 171	CAPS 150	
	n=74	5 day n=164	10 day n=154
Visit 3 (12-19 days after enrollment)			
No record	-	2	1
Cure	35 (47.3%)	99 (61%)	82 (54%)
Improved	24 (32.4%)	53 (38%)	60 (39%)
Failure	15 (20.3%)	10 (6%)	11 (7%)
Unevaluable	-	0	0
Post study			
No record	4	5	4
Unable to evaluate	2	8	3
Cured	49/68 (72%)	119 (79%)	123 (84%)
Improved		12 (8%)	9 (6%)
Failure	15/68 (22%)	13 (9%)	13 (9%)
Relapse	4/68 (5.8%)	7 (5%)	2 (1%)

- Post-study relapse rates were higher for the 5-day treatment regimens than for the 10-day regimen.
- Failure rates were substantially higher in CAPS171 than for either arm of CAPS 150. Given the older age and greater morbidity of the population in study CAPS 171, the poorer outcome appears consistent. Taking co-morbidity into account, the efficacy rates seen in study CAPS150 may be a truer representation of antibacterial efficacy of levofloxacin in patients with CAP, than the efficacy rates seen in study CAPS 171.
- Among 17 evaluable patients in study CAPS171 with creatinine clearances <50ml/min and dose adjustments to the study drug, the clinical failure rate was 29.4% compared with a failure rate of

17.5% in patients with creatinine clearances >50ml/min, suggesting inferior efficacy in this subpopulation.

b) Microbiological efficacy:

Clinical success rates (cure or improvement at test-of cure) are described for patient with pathogens identified at baseline.

Table c: Clinical success rates for the Pathogens of Primary Interest (pathogens seen in <10 patients are not included)

	CAPS 171	CAPS 150	
		5-day arm	10-day arm
Typical pathogens			
S pneumoniae	5/6	18/20	17/20
H influenzae	5/6	12/12	11/12
H parainfluenzae	6/7	10/10	8/9
Atypical pathogens			
M pneumoniae	11/12	26/27	24/26
C pneumoniae	4/5	13/15	6/6

Clinical efficacy appeared comparable for both regimens, in cases infected with the organisms shown above. (The small numbers of cases did not allow a meaningful statistical comparison.)

Dosing, regimen and administration:
The studies support a regimen of levofloxacin (oral or intravenous) 750mg QD for 5 days in patients with community acquired pneumonia.

Drug-drug interactions
These were not explored in this submission. Existing data in the label applies.

Special populations:
The studies in this submission contain adequate data supporting efficacy in women and racial minorities. The data suggest inferior efficacy in patients with creatinine clearances <50ml/min, in whom dose adjustment were made. Insufficient patients with positive blood cultures were included to evaluate the comparative efficacy of the regimen in this situation.

Clinical review

Introduction and background

Drug Established and Proposed Trade Name, Drug Class,
Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Levaquin is a chiral fluorinated carboxyquinolone antimicrobial agent, a member of the quinolone class. R.W. Johnson Pharmaceutical Research Institute (the aaplicant), is seeking approval for levofloxacin oral and intravenous formulations once daily for five days for the treatment of mild to severe community acquired pneumonia. Levofloxacin tablets/injectable are currently approved for the following indications in adults ≥18 years:

- Acute maxillary sinusitis (ABS)
- Acute bacterial exacerbation of chronic bronchitis (AECB)
- Community acquired pneumonia (CAP)
- Complicated skin and skin structure infections (cSSSI)
- Complicated urinary tract infections (UTI)
- Acute pyelonephritis (AP)
- Uncomplicated urinary tract infections (uUTI)
- Nosocomial Pneumonia

APPLICANT submitted sNDA 20634 in 2002 to support a new dosing regiment for the indication of treatment for mild to severe community-acquired pneumonia.

Proposed Labeling
(Indications and Usage, Dosage and Administration, Special Populations Section) for Levofloxacin (levofloxacin) tablets/injectable.

Levaquin tablets/injection are indicated for the treatment of adults (> 18 years of age) with mild, moderate and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Levaquin injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). The applicant has proposed new language for the DOSAGE and ADMINISTRATION and CLINICAL STUDIES sections of the label.

State of Armamentarium for Indication(s)

The list of antibiotics approved for the indication of Community Acquired Pneumonia is summarized in **Table 1.**

Table 1. Antibiotics Approved for Community Acquired Pneumonia

Brand (generic)	**Company**	**Organisms listed in label**	**Dose and Route**	**Duration**
Augmentin XR (Amoxacillin)	Glaxco Smith-Kline	**B-lactamase producing:** *M. catarrhalis* *H. parainfluenza* *K. pneumoniae* *S. aureus MSSA* *S. pneumoniae* (Penicillin MICS=2ug/ml)	2 tabs Q 12 h	7-10 days
Biaxin Granules	Abbott	*H. influenza*		

Brand (generic)	Company	Organisms listed in label	Dose and Route	Duration
(Clarithromycin)		*M. pneumoniae* *S. pneumoniae* *C. pneumoniae*	250 mg Q 12 h	7-14 days
Zithromax (Azithromycin)	Pfizer	*H.influenzae* *M. pneumonia* *C. pneumoniae* *S. pneumoniae*	500 mg po Q day then 250 mg po Q day	1 day 2-5 days
Avelox (Moxifloxacin)	Bayer	*H. influenza* *M. catarrhalis* *S. pneumoniae* *S. aureus* *K. pneumoniae* *M. pneumoniae* *C. pneumoniae*	400 mg iv/po Q day	7-14 days
Dynabac	Muro	*L. pneumophila* *M. pneumoniae* *S. pneumoniae*	500 mg po Q day	10 days
Floxin (Ofloxacin)	Ortho McNeil	*H. influenza* *S. pneumoniae*	400 mg iv/po Q 12 h	10 days
Invanz (Ertapenem)	Merck	*M. catarrhalis* *S. pneumoniae* PSSP *H. influenza* B-lactamase producing	1 g iv/im Q day	10-14 days
Levaquin (Levofloxacin)	Ortho McNeil	*S. aureus* *S. pneumoniae PSSP* *H. influenzae* *H. parainfluenzae* *K. pneumoniae* *M. catarrhalis* *C. pneumoniae* *L. pneumophila* *M. pneumoniae*	500 mg iv/po Q day	7-14 days
Omnicef (Cefdinir)	Abbott	*H. influenza* B-lactamase producing *S. pneumoniae PSSP* *M. catarrhalis* B-lactamase producing *H. parainfluenzae* B-lactamase producing	300 mg po q 12 h	10 days
Vantin	Pharmacia & Upjohn	*S. pneumoniae* *H. influenzae* B-lactamase producing	200 mg po Q 12 h	14 days
Zithromax (Azithromycin)	Pfizer	*C. pneumoniae* *L. pneumophila* *M. pneumoniae*	500 mg iv Q day followed	2-5 days then

Brand (generic)	Company	Organisms listed in label	Dose and Route	Duration
		S. aureus *S. pneumoniae* *H. influenzae* *M. catarrhalis*	by 500 mg po Q day	complete 7-10 days
Zosyn (Piperacillin)	Wyeth	*H. influenza* piperacillin resistant B-lactamase producing	3.375 g iv Q 6 h	7-10 days
Zyvox (Linezolid)	Pharmacia Upjohn	*S. pneumoniae PSSP* *S. aureus MSSA*	600 mg iv/po Q 12 h	10-14 days

Important Milestones in Product Development

CAP is the sixth leading cause of death in the U.S. and constitutes the most common cause of death due to an infectious disease. [1] It is estimated that 4 million cases of CAP are diagnosed annually, resulting in 600,000 hospital admissions which costs the health care system twenty three billion dollars a year. Mortality for CAP related admissions is estimated to be between 10-25%. [2,3] CAP is typically characterized by a new cough, auscultory findings consistent with pneumonia, presence of an acute infiltrate on chest x-ray and clinical signs and symptoms such as fever (or hypothermia), decreased breath sounds, chest pain, chills, mucopurulent sputum production and leukocytosis.

Streptococcus pneumoniae accounts for 20-60% of all adult cases of CAP, followed by Haemophilus influenzae and Moraxella catarrhalis. [1] Recently, studies have shown an increase in the etiology of CAP due to atypical pathogents such as Legionella pneumophila, Mycoplasma pneumoniae and Chlamydia pneumoniae with a concomitant decline in CAP due to S. pneumoniae. Furthermore, the emergence of antimicrobial resistance is making the treatment of CAP more difficult. The pathogens which commonly cause CAP, *S. pneumoniae, H. influenzae* and *M. catarrhalis*, are becoming more resistant to penicillin, cephalosporins, macrolides, chloramphenicol and trimethoprim/sulfamethoxazole (TMP-SMX), antimicrobials which in the past had been effective in treating CAP. [4,5]

Currently, the empiric treatment of CAP entails the use of broad-spectrum antibiotic regimens which should provide coverage against both the common pathogens (S.pneumoniae, M.pneumoniae, H.influenzae, C.pneumonia and L.pneumophila) and the less common pathogens (Staphylococcus aureus and Klebsiella pneumoniae) responsible for the etiology of CAP. Prior to the development of the fluoroquinolone class of antimicrobials, broad-spectrum empiric coverage for CAP was provided by combinations of two and sometimes three different antibiotics. The fluoroquinolones allow for broad-spectrum coverage with single agent use and therefore are now recommended for empiric monotherapy treatment of CAP. [6]

The FDA approved Levofloxacin (LEVAQUIN) on December 20, 1996 in NDA 20-634 for the treatment of skin, respiratory tract and urinary tract bacterial infections. In later submissions Levofloxacin was approved for the treatment of CAP (500 mg/day for 7-14 days), nosocomial pneumonia (750 mg/day for 7-14 days), acute exacerbation of chronic bronchitis (500mg/day), acute maxillary sinusitis (500 mg/day), complicated (mild to moderate) and uncomplicated UTIs (250 mg/day), acute pyelonephritis (250 mg/day) and complicated (500mg/day) and uncomplicated (750 mg/day) SSSIs.

Levofloxacin is currently approved for the treatment of CAP due to the following organisms: *S pneumoniae, H influenzae, H parainfluenzae, M pneumoniae, C pneumoniae, L pneumophila, S aureus, K pneumoniae and M cattarhalis*. The licensed dose is 500mg QD for a duration of 10 days. The current application seeks to shorten the duration of therapy for this indication to 5 days using a dose of 750mg QD. The applicant indicates that higher peak to MIC ratios using this regimen would allow shortening of the duration of therapy while reducing the likelihood of inducing bacterial resistance. This approach was

previously used for complicated skin and skin structure infections where a dose of 750mg QD for 7-14 days was approved in 2000 and for nosocomial pneumonia where a dose of 750mg for 7-14 days was approved in 2003.

More than 5800 subjects receiving either oral or intravenous levofloxacin have been studied in Phase 1 through 3 clinical trials conducted in North America. Subjects receiving 250 to 500 mg of levofloxacin on a daily basis experienced drug related adverse reactions during Phase 3 clinical trials at an incidence rate of 6.3%. 3.9% of subjects receiving levofloxacin therapy experienced adverse reactions that necessitated discontinuation of the therapy. The study population showed that the most frequent adverse events (>5%) noted during the therapy, but not necessarily due to levofloxacin, were nausea (7.2%), headache (6.4%) and diarrhea (5.6%).

Two clinical trials studied the safety profile of levofloxacin at a dose of 750 mg p.o. and/or i.v. given to normal volunteers for 7 days. [7,8] In addition, a recent Phase 3B clinical trial involving 850 subjects receiving levofloxacin at 750 mg i.v./p.o. was recently completed. The safety of levofloxacin at 750 mg i.v./p.o. was similar to that of the 500 mg i.v./p.o. formulation. The pharmacokinetics of levofloxacin has been found to be similar forboth healthy subjects and subjects with bacterial infections. [9] In addition, an open-label, multi-dose, randomized pharmacokinetic study showed good penetration of levofloxacin at doses of 500 and 750 mg resulting in high intrapulmonary concentrations in healthy, non-smoking adult subjects. [10,11]

Thus, based on levofloxacin's known safety profile, pharmacokinetics and antibacterial spectrum it has been proposed that a regimen of 750 mg i.v./p.o. on a daily basis for five days would be an effective treatment for patients with mild to severe CAP caused by susceptible pathogens and that drug-related adverse events would be mild.

Other Relevant Information

Levoquin is approved world wide in 57 countries, including the USA.

Important Issues with Pharmacologically Related Agents

The quinolones, as a class of drugs, has shown adverse effects that include tendon related disorders, QT interval changes and phototoxicity. Adverse events that may be related to each therapeutic quinolone agent include "temafloxacin syndrome", liver failure (due to trovafloxacin) and dysglycemic reactions (due to gatifloxacin).

Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and /or Other Consultant Reviews.

Microbiology: the reviewer concludes that the 750 mg dose seemed to have more of an effect against the typical pathogens within the first 12-21 days of the study; but by day 17-24 of the study, the effectiveness of the 500 mg 10 day and 750 mg 5 day courses were almost equivalent.

Pharmacology and Toxicology: no clinically significant findings.

Statistics: refer to Dr. Jyoti's Statistical Review for sNDA 20-634.

Chemistry: no clinically significant findings.

Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There is rapid and complete (99%) absorption of levofloxacin upon oral administration and peak plasma concentrations are achieved within one to two hours after oral dosing. When a single intravenous dose of levofloxacin at 500 mg or 750 mg was administered to healthy volunteers, the mean plasma concentration was 6.2 µg/ml and 11.5 µg/ml respectively. After single or multiple oral or i.v. dosing regimens, the pharmacokinetics of levofloxacin is linear with steady-state conditions reached within 48 hours after a 500 mg or 750 mg once-daily regimen. **(Table 2)**

Table 2. Peak and Trough Plasma Concentrations after Multiple Levofloxacin Dosing (oral and intravenous)

Route	Oral		Intravenous	
Dose (multiple once daily dosing)	500 mg	750 mg	500 mg	750 mg
Peak Plasma Conc. µg/ml	5.7	8.9	6.4	12.1
Trough Plasma Conc. µg/ml	0.5	1.1	0.6	1.3

If levofloxacin tablets are administered with food, there is a slight (one hour) delay to the time of peak concentration and a 14% decrease in the peak plasma concentration. Therefore, oral dosing of levofloxacin can be administered without regard to food. Levofloxacin has widespread distribution into body tissues especially the lungs. After a single 500 mg oral dose, lung tissue concentrations were 2-5 times higher than plasma concentrations over a 24 hour period. In vitro, levofloxacin shows 24-38% protein binding, mainly to serum albumin. Serum protein binding of levofloxacin is independent of the drug concentration.

There is limited metabolism of Levofloxacin in humans. After oral administration, 87% of the given dose was primarily excreted as unchanged drug in the urine within 48 hours while less than 4% of the dose was recovered in feces in 72 hours. Levofloxacin metabolites, desmethyl and N-oxide which have no significant pharmacologic activity, were recovered in the urine in less than 5% of the original administered dose. The mean terminal plasma elimination half-life (T1/2) of levofloxacin is about 6 to 8 hours after single or multiple doses of the drug administered orally or intravenously. Administration of oral levofloxacin to elderly subjects (66-80 years old) resulted in T1/2 of 7.6 hours compared to 6 hours for younger adults. The applicant reports that the variation was due to a difference in renal function status between the two age groups and did not consider the difference to be clinically significant. Levofloxacin is excreted into the urine by both tubular secretion and glomerular filtration. Race and age do not seem to affect the pharmacokinetics of levofloxacin except as discussed previously with regard to T1/2.

Co-administration of [redacted] sults in a [redacted] .e renal clearance of levofloxacin respectively. Antacids, sucralfate, metal cations and multivitamins with zinc may lower system levels of levofloxacin, therefore concomitant administration of these medications should be avoided during levofloxacin treatment. Monitoring of plasma levels for agents such as theophylline, cyclosporine, digoxin and warfarin is recommended when taken with levofloxacin. In diabetics, the use of blood glucose lowering agents should be monitored due to reports of altered blood glucose levels during the use of quinolone antibiotics. The use of NSAIDS during levofloxacin therapy may increase the risk of seizure activity.

Pharmacodynamics

Clinical pharmacology studies have been previously submitted in NDA 20-634 and 20-635. No new pharmacodynamic issues were raised with this supplement.

Description of clinical data and sources:

The present submission includes one randomized, double-blind study comparing the approved 500mg QD 10-day regimen with the proposed 750mg QD 5-day regimen for mild to moderate community acquired pneumonia. A non-comparative supportive study using the proposed regimen in patients with CAP is also provided to bolster the numbers of individual pathogens. The applicant has provided additional safety data on the proposed dosing regimen, which was derived from a study of patients with febrile neutropenia.

Table 3. Overview of Clincial studies to support the efficacy of levofloxacin for the treatment of community acquired pneumonia (CAP)

Protocol	Geographic Location	Study Design	Treatment Regimen(s)	Subjects/Clinical Eval/Micro Eval	Mean Age (yr) (Range)
Pivotal CAPSS-150	Multicenter (U.S.A.)	Double-blind, randomized Non-inferiority	Levaquin 750 mg i.v. or p.o. qd x 5 days Levaquin 500 mg i.v. or p.o. qd x 10 days	256/198/103 265/192/92	53.1 (18-86) 55.3 (18-89)
CAPSS-171	Multicenter (U.S.A.)	Open-label Non-compara-tive	Levaquin: 750 mg i.v. or p.o. qd x 5 days	123/74/34	59.6 (22-93)

Postmarketing Experience

The applicant's postmarketing experience reported in the submission included safety tables from the USA and International pharmacovigilance database for adverse events.

Literature Review on Safety Profile of Fluoroquinolones

Summary of fluoroquinolone related adverse effects

- **Gastrointestinal Effects**: nausea, vomiting, diarrhea, abdominal discomfort
- **CNS Effects**: headaches, dizziness, sleep disturbances, hallucinations, psychotic reactions, depression, seizures, tremors, restlessness
- **Dermatologic Effects**: phototoxicity, maculopapular/urticarial rash,
- **Hematologic Effects**: hemolytic anemia, severe hemolysis
- **Hepatic Effects**: inhibition of cytochrome P-450 (CYP-450) enzyme system, liver failure
- **Cardiac Effects:** QTc prolongation
- **Metabolic Effects**: hypogylcemia
- **Renal Effects**: renal failure
- **Musculoskeletal Effects**: arthropathy in juvenile dogs, tendon lesions, arthralgia

- **Immunologic Effects**: anaphylactoid reactions, life-threatening hypersensitivity reactions
- **Drug Interactions**: with theophylline and methylxanthines, NSAIDs, antiarrythmic agents: class IA (eg, quinidine, procainamide), class III (eg, amiodarone, sotalol), warfarin, digoxin

Table 4. Incidence of the most common drug-related adverse events occurring with the newer fluoroquinolones, based on package inserts.
Source: Bertino Joseph, Fish D. The Safety Profile of the Fluoroquinolones. Clinical Therapeutics. 2000; 22:798-817.

Event (%)	Ciprofloxacin	Levofloxacin	Sparfloxacin	Trovafloxacin	Lomefloxacin
Nausea	5.2	1.2*	4.3	8.0	3.7
Diarrhea	2.3	1.2*	4.6	2.0	1.4
Taste perversion	0.02	0.2	1.4	-	< 1.0
Headache	1.2	0.1	4.2	5.0	3.2
Dizziness	< 1.0	0.3	2.0	11.0	2.3
Phototoxicity	0.4	<0.1	7.9	<0.03	2.4

* In the approved label Levofloxacin event % data for nausea and diarrhea were 1.3% and 1.0 % respectively.

Clinical review methods :

Differences in study populations and efficacy rates did not allow pooling of the results for studies CAPS 150 and CAPS 171. For this reason these studies are reviewed separately below. The primary evaluation of efficacy is based on study CAPS 150. Study CAPS 171 is non-comparative and provides supportive data.

Source data were analyzed by the reviewer using JMP 4.04 software. The data had been electronically submitted (\\cdsesub1\n20634\s_028\2002-12-20.) Results were compared with those provided by the applicant in the study report. Additional data were extracted from the text provided in individual case report forms, when this information was not present in the data tables.

The trials were conducted in accordance with accepted ethical standards.

Integrated Review of Efficacy

The efficacy of the proposed 5 day regimen of levofloxacin (750mg QD) was tested in 392 clinically evaluable patients participating in 2 clinical trials (CAPS 150 randomized placebo controlled comparing the proposed regimen with the approved regimen of 500mg QD for 10 days and CAPS 171- open label non-comparative study using the proposed regimen only).
Patients included those with mild to moderate community acquired pneumonia with compatible radiological and clinical features. (See study reviews for details).
Seventy-four of the 392 patients were participants in CAPS 171, and were similar to those in CAPS 150 except for the fact that they were sicker at entry when evaluated using the "Fine score", the age of the patients was greater, and patients were included with more severe renal dysfunction where dosing adjustment was required.
The test-of- cure was 17-21 days post initiation of therapy for CAPS 150 and 12-16 days post therapy for CAPS 171.
The primary outcome variable was clinical success (which included clinical cures and clinical improvements without the need for further antimicrobials). The outcome for each patient was determined by the clinical judgment of the investigators.
A visit 31-38 days after study enrollment was designed to detect relapses.
Microbiological efficacy was determined in the small portion of patients with pathogens identified at entry.

Study Quality

Many enrolled patients could not be included in the clinically evaluable populations of both studies.
In CAPS 150, 102 of the 530 patients recruited to the study failed to satisfy the inclusion criteria requiring a fever or abnormal white blood count, and could not be evaluated.
In CAPS 171, 49 of 123 patients recruited to the study could not be evaluated, 19 or these for failing to present during the "test-of-cure window".
Only 12 patients in the two studies combined were lost to follow-up.

Efficacy

Efficacy results are tabulated below for each arm of CAPS150 and for CAPS 171. The efficacy analyses addressed include:
a) Clinical:

- Clinical success rate (cure+improvement) [primary endpoint]
- Clinical cure rates, clinical improvement rates, clinical relapse rates.

  Subgroups:
  - Severity of disease
  - Blood culture positive
  - Renal dysfunction
  - Deaths

b) Microbiology

- Clinical and microbiological responses
- Superinfections

a) Clinical success rate (CAPS171 and CAPS 150)

Table 5: Clinical success rates

	CAPS 171[1]	CAPS 150[2]	
		5 day	10 day
Clinical success	59/74 (79.7%)	146/159 (92%)	141/154 (92%)

1 test of cure 12-16 days post initiation of therapy
2 test of cure 17-21 days post initiation of therapy

For CAPS 150, 95% confidence interval (10- day minus 5-day =) -6.4% to 5.9%

Clinical cure rates, clinical improvement rates, clinical relapse rates

Table 6: clinical efficacy (clinically evaluable population)

	CAPS 171	CAPS 150	
	n=74	5 day n=164	10 day n=154
Visit 3 (12-19 days after enrollment)			
No record	-	2	1
Cure	35 (47.3%)	99 (61%)	82 (54%)
Improved	24 (32.4%)	53 (38%)	60 (39%)
Failure	15 (20.3%)	10 (6%)	11 (7%)
Unevaluable	-	0	0
Post study			
No record	4	5	4
Unable to evaluate	2	8	3
Cured	49/68 (72%)	119 (79%)	123 (84%)
Improved		12 (8%)	9 (6%)
Failure	15/68 (22%)	13 (9%)	13 (9%)
Relapse	4/68 (5.8%)	7 (5%)	2 (1%)

Subgroups
Severity of disease:

Table 7: Failure rates by Fine risk category:

	Milder			More severe		
	CAPS 171_1	CAPS 150_2		CAPS 171_1	CAPS 150_2	
		5-day	10-day		5-day	10-day
Failure rate	5/42 (11.9%)	8/98 (8%)	4/82 (5%)	10/32 (31.3%)	5/61 (8%)	9/72 (13%)

1 test of cure 12-16 days post initiation of therapy
2 test of cure 17-21 days post initiation of therapy

MO comment: The disparately high failure rate in CAPS 171 was largely due to the patients with more severe disease.

Blood culture positive:

Table 8: Clinical success rates in patients with positive blood cultures at baseline:

	CAPS 171	CAPS 150	
		5-day arm	10-day arm
S pneumoniae	3/5 (2 unevaluable)	4/7	4/5 (2 unevaluable)
*E coli**	-	3/3	-
S aureus	-	-	(1 unevaluable)
*P putida**, *S pyogenes**	1/1	-	-
Coagulase negative* *S aureus*	1/1	-	-

* Role as a pneumonic pathogen is unusual

Renal dysfunction

Table 9: Outcome according to baseline renal function (CAPS 171 only)

	Normal renal function	Renal dysfunction
Cured	32/57 (56%)	3/17 (17.6%)
Improved	15/57 (26%)	9/17 (52.9%)
Failed	10/57 (17.5%)	5/17 (29.4%)

One third of the failures in this study occurred among the 17 patients with renal failure (23% of the study population) suggesting that patients with renal failure accounted significantly for the high failure rate in this study. However, the 17.5% failure rate in patients with normal renal function in this study is still higher than the failure rate seen in study CAPS150 of 8% among patients allocated to the 5-day treatment arm.

Deaths:

Table 10: Deaths among clinically evaluable patients

	CAPS 171[1]	CAPS 150[2]	
		5 day	10 day
Deaths	6/74 (8.1%)	5/174 (2.8%)	9/165 (5.4%)

None of the deaths appeared related to treatment failure. The higher death rate in study CAPS171 may be yet another sign that CAPS171 recruited a sicker patient population.

Clinical and microbiological responses

Table 11: Clinical success rates for the Pathogens of Primary Interest

	CAPS 171	CAPS 150	
		5-day arm	10-day arm
Typical pathogens			
Strep pneumo	5/6	18/20	17/20
H influenzae	5/6	12/12	11/12
H parainfluenzae	6/7	10/10	8/9
Atypical pathogens			
M pneumoniae	11/12	26/27	24/26
C pneumoniae	4/5	13/15	6/6

Superinfections:

Table 12: Bacterial superinfections

	CAPS 171	CAPS 150	
		5-day arm	10-day arm
S pneumoniae	-	3	1
Methicillin-resistant *S. aureus* (MRSA)	1	-	3
Candida albicans	-	-	1
P maltophilia	-	-	1
Mycobacterium	1	-	-

Of all the superinfections, those with *S pneumoniae* were most compatable with relapses in cases where initial cultures may have failed to detect *S pneumoniae*. Such *S pneumoniae* superinfections were more frequent in the 5-day arm than the 10-day arm of CAPS 150.

Conclusions
CAPS 150 demonstrated the equivalent efficacy of levofloxacin 750mg QD x 5 days to levofloxacin 500mg QD x 10 days. The limitations of the study included the large percentage of unevaluable patients in both arms because of failure to satisfy entry criteria.

The most likely evidence of inadequate therapy would have been relapses after initial responses. While this was not captured by the primary endpoint (17-21 days after initiation of therapy), clinical relapses did indeed appear more frequently in the short-course arm at the post-study visit. The study was not powered to give this observation statistical significance.

No particular characteristic (severity of disease, specific organism, blood culture result) was identified that appeared to predict clinical relapse.

Very small numbers of evaluable patients were identified with microbiological pathogens at the time of enrollment. For these few patients, numerical rates for clinical success or microbiological eradication were high in both study arms.

Among the subgroup of patients with severe disease based on Fine score at entry, success rates for the short course arm at the test-of-cure were equivalent to those of the conventional treatment arm

There were too few patients in the study with positive blood cultures at entry to determine comparative efficacy in this subpopulation. Numerically, there were more failures in the short-course arm than the conventional-treatment arm, among patients with *S pneumoniae* on blood culture.

Fewer patients died in the short course arm than in the conventional treatment arm. None of the deaths in the study appeared to result from a failure of antimicrobial treatment.

Study CAPS 171 was an uncontrolled study with a substantially higher failure rate than the failure rate seen for the proposed regimen in CAPS150. For this reason the reviewer elected not to pool the results of the two studies.

The poorer success rates in this study were probably due to the following factors. Patients enrolled in CAPS171 were older that those in CAPS 150, there were more patients with severe disease at entry based on Fine score, and patients were included with more severe renal dysfunction for which dosage adjustments were made to the levofloxacin regimen.

The subgroup of patients in this study with severe renal dysfunction (creatinine clearance below 50ml/min) showed a much higher failure rate than the rest of the study patients. While this may be due to inadequate drug levels as a result of the dose adjustments, the reviewer could not rule out the potential confounding effect of renal failure on the investigators' assessment of clinical response.

On the basis of these efficacy results, the reviewer recommends approval of the proposed regimen as an alternative to the approved regimen. Both regimens should be included in the labei. The clinical studies section should include data on the relapses that were more frequent in the short course arm. The organisms for which sufficient evidence of efficacy was provided should be listed.
Regarding the concern about increased failure rates in patients with dosage adjustments for renal dysfunction, the reviewer proposes that the company perform a phase 4 study, confirming satisfactory PK response in subjects with renal dysfunction and dosage adjustments. Pending these data, the clinical studies section of the label should reflect the high failure rates seen in the subgroup of patients with creatinine clearances below 50ml/min.

Integrated Review of Safety

Brief Statement of Conclusions

Levaquin, a member of the quinolone class of antimicrobials, is a fluorinated carboxyquinolone agent. In the USA, Levaquin is approved for community-acquired pneumonia, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, complicated skin and skin structure infections, acute pyelonephritis and both comp licated and uncomplicated urinary tract infections.

The applicant is seeking approval for the use of Levofloxacin 750 mg once daily for five days in the treatment of mild to severe community-acquired pneumonia in adults. In 2001 two NDA's (NDA 20-634/635) were submitted to evaluate Levaquin for the indication of Nosocomial Pneumonia. The safety profile for Levaquin had been studied through the clinical trials that were performed to demonstrate its efficacy and safety under the original NDA.

The MO presents the safety data from Study-CAPSS-150 and Study-CAPSS-171. The baseline demographic characteristics of the two treatment groups in the CAPSS-150 study were comparable. The CAPSS-150 population was generally younger than the CAPSS-171 group (mean age 54.2 vs. 59.6). The percentages of males and females in the CAPSS-150 study was comparable to the CAPSS-171 group. In both studies most of the subjects were Caucasian followed by Blacks, Hispanics and Asians. The rate of at least one treatment emergent adverse event reported in the CAPSS-150 study for the 750 mg group was 148/256 (57.8%) vs.158/265 (59.6%) in the 500 mg group. In the CAPSS-171 group the rate was 73/123 (59.3%).

Overall, the most common AEs associated with the use of levofloxacin in the 750 mg group versus the 500 mg group in the CAPSS-150 study were found in the gastrointestinal system (20.3% vs. 21.9%), general disorders (16.4% vs. 21.9%), respiratory system disorders (15.2% vs. 17.4%) and psychiatric disorders (12.1% vs. 15.8%). In the 750 mg group central and peripheral nervous system disorders accounted for 12.1% of AEs.

In the CAPSS-171 study the most common AEs were found in the gastrointestinal system (26%), psychiatric disorders (25.2%), general disorders of body as a whole (22.8%), respiratory system (19.5%) and metabolic and nutritional disorders (13.8%).

In general, adverse events occurring in greater than 2% of patients in both the CAPSS-150 and CAPSS-171 studies were similar to the known adverse events specified in the levofloxacin label.

The rate of serious treatment-emergent adverse events in the CAPSS-150 study for the 750 mg group versus the 500 mg group was 25/256 (9.8%) vs. 37/265 (14%) respectively. In the CAPSS-171 group the rate of serious AEs was 18/123 (14.6%).

The rate of discontinuation of the study drug due to an AE in the CAPSS-150 study was 18/256 (7.0%) in the 750 mg group versus 22/265 (8.3%) in the 500 mg group. In the CAPSS-171 group the rate of discontinuation was 7/123 (5.7%).

The total death rate in the CAPSS-150 study for the 750 mg group versus the 500 mg group was 5/256 (1.9%) vs. 9/265 (3.4%) respectively. In the CAPSS-171 study the death rate was 6/123 (4.9%). None of the deaths in either of the study groups was considered related to the study drug.

There was no evidence of QT prolongation among the adverse events reported for subjects in the CAPSS-150 or CAPSS-171 studies.

Most laboratory abnormalities reported in the CAPSS-150 and CAPSS-171 studies were mild or moderate in severity. Thirty (11.7%) subjects in the 750 mg group and thirty-three (12.5%) subjects in the 500 mg group had one or more abnormal laboratory values during treatment with the study medication.

In the CAPSS-150 study the most common reported laboratory abnormalities in the 750mg group were elevated glucose (3.6%) and SGPT (3.6%); in the 500 mg group it was decreased lymphocytes (3.1%) and decreased glucose (3.1%). Seventeen (13.8%) subjects in the CAPSS-171 study reported one or more markedly abnormal laboratory values observed for hematology (hemoglobin, decreased lymphocytes and neutrophils) and blood chemistry (BUN, SGPT, glucose and creatinine) parameters.

Description of Patient Exposure

For the CAPSS-150 study, data provided by the applicant on the extent of exposure based on the ITT population in terms of treatment and route of administration (i.v. or oral) is summarized in tables 29 (levofloxacin 750 mg group) and 30 (levofloxacin 500 mg group).

In the levofloxacin 750 mg group, the mean duration of treatment was 4.8 days (range 1 to 7 days) and the mean number of active doses was 4.8 (range 1 to 7 doses). One subject received more than five doses of active medication. This was due to an error in protocol directions in terms of administration of oral medication to subjects who had initially received i.v. medication. Twenty-four subjects treated only with i.v. medication received a mean of 4.0 active doses (range 1 to 5 doses) for a mean of 4.0 days of treatment (range 1 to 5 days). One hundred forty-seven subjects treated only with p.o. doses received a mean of 4.8 active doses (range 1 to 5 doses) for a mean of 4.8 days of treatment (range, 1 to 6 days). The remaining 85 subjects in the 750 mg group received i.v. study medication initially and later were switched to oral therapy.

In the levofloxacin 500 mg group, the mean duration of treatment was 8.8 days (range 1 to 17 days) with the mean number of active doses administered being 8.8 doses (range 1 to 10 doses). If subjects failed to take levofloxacin on a daily basis for 10 consecutive days as instructed to do so, they were treated for more than 10 days with the study drug. Twenty-four subjects who received only i.v. doses of study medication were administered a mean of 3.8 active doses (range 1 to 10 doses) over a mean of 3.8 days duration (range 1 to 10 days). One hundred forty-seven subjects who were administered only p.o. doses of the study medication received a mean of 9.1 active doses (range 1 to 10 doses) for a mean of 9.1 days of treatment (range 1 to 17 days). The remaining one hundred and one subjects in the 500 mg group received i.v. therapy initially and then were later changed to p.o. therapy.

For the CAPSS-171 study the applicant provided extent of exposure data for all safety evaluable subjects: the mean duration of levofloxacin treatment was 4.9 days (range 1 to 10 days). The mean number of active doses was 4.3 doses (range 1 to 6 doses).

Demographics

Safety data from Study-CAPSS-150 and Study CAPSS-171.
Study-CAPSS-150 consists of two treatment groups, levofloxacin 750 mg once a day for five days and the comparator group, levofloxacin 500 mg once a day for 10 days. Study CAPSS-171 consists of the non-comparator group. The baseline demographic characteristics of the CAPSS-150 population showed a generally younger group (mean age = 54.2; range= 18-89) than the CAPPS-171 non-comparator group (mean age= 59.6; range= 22-93). There were comparable percentages of males in the CAPSS-150 and CAPSS-171 studies (58.7 vs. 57.7 respectively) as well as females (41.3 vs. 42.3 respectively).

In both studies the majority of subjects were Caucasian (68.6% in CAPSS 150 vs 65% in CAPSS 171); with Blacks comprising 21.8% of subjects in CAPSS-150 and 26.8% in CAPSS-171; Hispanics comprising 7.6% of subjects in CAPSS-150 and 4.9% in CAPSS-171 and Asians comprising 1.3% in CAPSS-150 and 3.3% in CAPSS-171.

All Adverse Events

CAPSS-150

Overall, at least one treatment associated adverse event starting up to 14 days after the last dose of levofloxacin was reported in 148 (57.8%) of the 256 safety-evaluable subjects who received levofloxacin 750 mg and 158 (59.6%) of the 265 safety-evaluable subjects in the 500mg group of the CAPSS-150 study. The overall rates of adverse events did not appear significantly different between the two treatment groups. Within the levofloxacin 750 mg group, two subjects had adverse events between 15 and 19 days after the last active dose. The rate of adverse events through 19 days posttherapy was 58.6% in that group.

The most common AEs associated with the use of levofloxacin through day 14 posttherapy in 10% or more of the subjects in the 750 mg group of the CAPSS-150 study were related to the gastrointestinal system (20.3%), general disorders (16.4%), respiratory system disorders (15.2%), central and peripheral nervous system disorders (12.1%) and psychiatric disorders (12.1%). Ten percent or more of the subjects in the 500 mg group had adverse events related to the gastrointestinal system (21.9%), general disorders (21.9%), respiratory disorders (17.4%) and psychiatric disorders (15.8%). (see **Appendix 2**). With the exception of the white cell and reticuloendothelial (RES) system, there were no statistically significant differences reported by the applicant for all body systems with respect to the 750 mg and 500 mg treatment groups. Occurrence of adverse events in the white cell and RES system was 0% in the 750 mg group and 1.9% in the 500 mg group. Levofloxacin related adverse events up to 19 days posttherapy for the 750 mg group did not show a marked difference in results.

CAPSS-171

The CAPSS-171 study showed that 73 (59.3%) of the 123 subjects who received levofloxacin had at least one treatment-emergent adverse
event. Subjects in this group had AEs associated with the gastrointestinal system (26%), psychiatric disorders (25.2%), general disorders of body as a whole (22.8%), respiratory system (19.5%) and metabolic and nutritional disorders (13.8%) (see **Appendix 3**).

CAPSS-150 and CAPSS-171 AEs compared to the Levofloxacin Label

Overall, the adverse events which occurred in greater than 2% of patients in the CAPSS-150 and CAPSS-171 studies were similar to the known adverse events associated with levofloxacin therapy as indicated in the label. Constipation, headache, nausea and insomnia had incidence rates > 4% in both treatment groups of the CAPSS 150 study. The incidence of constipation was similar in the 750 mg group (5.1%) and the 500 mg group (4.5%). The incidence was higher in the 750 mg group than in the 500 mg group for headache (8.6% vs. 5.7%), nausea (8.6% vs. 5.7%) and vomiting (5.1% vs. 2.6%). Other frequently reported adverse events (incidence rates > 4%) included diarrhea (6.0%) in the levofloxacin 500 mg group. The incidence for this AE was lower in the 750 mg group (3.1%). Adverse events with noticeably different rates in the 750 and 500 mg groups of the CAPSS-150 study were pain (1.2% vs. 3.4%) and epistaxis (2.0% vs. 0.0%).

Subjects in the CAPSS-171 study showed incidence rates for headache of 6.5%; nausea 6.5% and vomiting 2.4%. Two adverse events had the highest incidence rates:constipation (9.8%) and insomnia (17.9%). The applicant reports that the incidence of insomnia in the CAPSS-171 study was higher than the 4.6% insomnia rate reported in previous Phase 3 trials of levofloxacin. Explanations offered by the applicant for the higher than expected rate of insomnia include: 1) most of the subjects reporting insomnia were hospitalized patients, 2) two investigators had standing orders in the hospital for concomitant medications as sleep aids; there was a total of 9 subjects between these 2 investigators who received concomitant medication for insomnia. 3) 9 of the 22 subjects who reported insomnia, only had it for 1 day, which resulted in more events of insomnia but didn't reflect a persistent drug-related problem. 4) the higher incidence of insomnia may in part be due to the underlying respiratory disease state which can interfere with normal sleep patterns. 5) a majority of the patients were receiving multiple concomitant meds, some of which are associated with sleeplessness.

Other frequently occurring adverse events in the CAPSS-171 subjects included chest pain (7.3%), anxiety (6.5%), and pleural effusion (5.7%). This may be due, in part, to the older age of the subjects (mean age= 59.6 vs. 54.2) who in general constituted a sicker population compared to the CAPSS-150 group. Alternatively, these adverse events may be manifestations of the subjects' pneumonia rather than related to the study medication. In the CAPSS-171 group diarrhea had an incidence of 4.9%.

Table-13. Incidence of Frequently Reported Adverse Events (>2%) from CAPSS-150, CAPSS-171 and Approved Levofloxacin Label.

Adverse Event	CAPSS-150		CAPSS-171	Approved Label
	750 mg	500 mg		
Headache	8.6	5.7	6.5	6.2
Constipation	5.1	4.5	9.8	3.5
Nausea	8.6	5.7	6.5	7.1
Diarrhea	3.1	6.0	4.9	5.5
Vomiting	5.1	2.6	2.4	2.4
Insomnia	7.0	10.6	17.9	5.1
Pain	1.2	3.4	4.1	
Epistaxis	2.0	0		
Chest Pain	2.3	2.3	7.3	
Anxiety	1.2	2.6	6.5	
Pleural Effusion			5.7	

Drug Related Adverse Events:

CAPSS-150

The applicant reports that events considered probably or very likely re lated to the study drug occurred in eighteen (7.0%) subjects in the 750 mg group and fifteen (5.7%) subjects in the 500 mg group. In the 750 mg group, the most common drug related AEs were nausea (five subjects) and rash and condition aggravated (two subjects each). Two subjects in this group had drug-related adverse events (tremor and nausea) that were considered to be of marked severity. In the 500 mg group, the most common AEs were rash (three subjects) insomnia, diarrhea, moniliasis and moniliasis genital (two subjects each). Two subjects in this group experienced markedly severe drug-related adverse events consisting of agitation and confusion.

CAPSS-171

The applicant reports that five (4.1%) subjects who received the study medication had a total of six drug-related adverse events. One subject (106001) had two drug-related adverse events (diarrhea and dehydration) that was considered by the investigator to be of marked severity. This subject was an 81 year old Caucasian female hospitalized with pneumo nia who received 5 days of levofloxacin 750 mg i.v. After receiving all doses of the study medication she became dehydrated on the third posttherapy day (3 days after the last day of study drug administration) and experienced diarrhea on the fourth posttherapy day. The duration of the dehydration and diarrhea was 8 and 3 days respectively in this patient. The diarrhea did not respond to loperamide therapy and the patient required hospitalization on the sixth posttherapy day for rehydration with i.v. fluids and metronidazole treatment. Stool samples were negative for Shigella, Campylobacter, Clostridium toxin and Salmonella. During her hospitalization the patient responded to therapy and was discharged after a 1 day admission.

Severe Adverse Events

CAPSS-150

Adverse events of mild or moderate severity were found in both treatment groups of the CAPSS-150 study and the CAPSS-171 study and did not seem to be related to the study drug. Treatment emergent adverse events of marked severity occurred in both treatment groups of CAPSS-150. There were eighteen subjects in the levofloxacin 750 mg group (12.2% of subjects with adverse events) and twenty-eight subjects in the levofloxacin 500 mg group (17.7% of subjects with adverse events). Events of marked severity occurred most often in the respiratory system (4 subjects in the 750 mg group and 14 subjects in the 500 mg group), general disorders (5 subjects in the 750 mg group and 12 subjects in the 500 mg group), heart rate and rhythm disorders (2 in the 750 mg group and 5 in the 500 mg group) and cardiovascular disorders (1 in the 750 mg group and 4 in the 500 mg group).

CAPSS-171

In the CAPSS-171 study eighteen (14.6%) subjects had one or more adverse events of marked severity. Twenty-four markedly severe adverse events in 14 subjects were serious adverse events. Discontinuation of therapy was required in two subjects with three markedly severe adverse events.

Overall, seven (5.7%) subjects had adverse events that resulted in discontinuation of treatment. Allergic reaction was the only adverse event leading to discontinuation that occurred in more than one subject (subjects 3002 and 22003). Ten adverse events led to discontinuation of treatment two were reported by the applicant to be very likely related to the study drug: allergic reaction (subjects 3002 and 22003). Four adverse events were reported to be possibly related to the study drug: diarrhea and nightmares (subject 57001), worsened ankle pain (subject 89001) and worsening of liver enzymes (subject 9003). All other adverse events leading to discontinuation of the study drug were considered not related or of doubtful relationship to the study medication. For adverse events with a known outcome, all AEs resolved after discontinuation of levofloxacin. Two adverse events, insomnia (subject 22003) and Herpes simplex (subject 4001) reportedly had unknown outcomes.

Serious Adverse Events

Investigators in the CAPSS-150 and CAPSS-171 study evaluated the severity and the relationship of all adverse events to the study medication. Events that were thought to have a "probable" or "definite" relationship to levofloxacin treatment were considered to be drug related adverse events. The applicant defined a serious adverse event as "any event that was fatal, immediately life-threatening, required or prolonged inpatient hospitalization, caused permanent or significant disability, was a congenital anomaly or was deemed medically important".

CAPSS-150

Serious treatment-emergent adverse events were reported by the applicant for twenty-five (9.8%) subjects in the levofloxacin 750 mg group and thirty-seven (14.0%) subjects in the levofloxacin 500 mg group. In the 750 mg group the most frequently reported serious adverse events were condition aggravated (i.e. worsening of pneumonia, pneumonia aggravated, new occurrence of pneumonia, recurrent pneumonia, aggravated condition and COPD exacerbation), myocardial infarction (1.6%), chronic obstructed airway disease (1.2%) and respiratory insufficiency (1.2%). In the 500 mg group, the most frequently reported serious adverse events were condition aggravated (3.4%), dyspnea (2.3%), cardiac arrest (1.1%), asthma (1.1%), pleural effusion (1.1%) and respiratory insufficiency (1.1%). The applicant reports that the investigators considered most of the serious adverse events to be unrelated or of doubtful relationship to the study drug. In the 750 mg group, three cases of condition aggravated and one case of hypertonia were considered possibly, probably or very likely drug related. In the 500 mg group, two cases of condition

aggravated and one case of depression aggravated were considered possibly, probably or very likely drug related.

CAPSS-171

Serious treatment emergent adverse events were reported by the applicant for eighteen (14.6%) subjects. Serious adverse events that occurred in more than one subject were condition aggravated (three subjects); cardiac failure (three subjects); pulmonary carcinoma (three subjects); cardiac arrest (two subjects); and allergic reaction (two subjects). Five subjects had serious adverse events between 15 and 30 days after the last dose of levofloxacin. Of 45 serious adverse events reported by 20 subjects, two were reported by the applicant to be very likely related to the study drug: allergic reaction (subjects 3002 and 22003). Subject 106001 had dehydration and diarrhea which was considered probably related to the study drug. One serious adverse event in subject 310001, aggravated condition (incomplete resolution of pneumonia), was judged possibly related to the study drug. All other serious adverse events were considered not related or of doubtful relationship to the study drug. According to the applicant, all serious adverse events resolved within 35 days of onset.

Deaths

CAPSS-150

Death rates for CAPSS-150 subjects were reported from study-admission to the poststudy period. None of the deaths in the study were attributed to study drug. Five (1.9%) subjects who received levofloxacin 750 mg and nine (3.4%) subjects who received levofloxacin 500 mg died between study admission and poststudy (see **Appendix 4**). Two subjects (one in each treatment group) died due to worsening Community Acquired Pneumonia and an additional four subjects (three in the 500 mg group, one in the 750 mg group) died due to respiratory failure or insufficiency. In the 750 mg group, two of the deaths occurred within 14 days after the last dose of active medication and the other three deaths occurred > [redacted] posttherapy. In the 500 mg group, seven of the deaths occurred up to eight days posttherapy and the remaining two occurred > [redacted] posttherapy. The age of the subjects in the 750 mg group ranged from 62-76 and represented 4 males and 1 female. The age of the subjects in the 500 mg group ranged from 48-79 and represented 7 males and 2 females. After careful review of the case histories of the subjects who died, the MO concurs with the applicant that the deaths in the two treatment groups were not due to the study drug.

CAPSS-171

In the CAPSS-171 study six subjects died during the study (see **Appendix5**). The age of the subjects who died ranged from 31-83 years old and consisted of 4 males and 2 females. Five subjects who had adverse events leading to death were not attributed to study drug or of doubtful relationship (subject 4002) to the study medication.

Subject 4002 was a 50 y.o. Caucasian female who was treated with 750 mg p.o. daily of levofloxacin for 6 days. Four days after initiating the study drug the patient was found to have dullness at the right lung base without any associated symptoms. One day after her last dose of study medication she was found to have a large right pleural effusion with a previous right upper lobe infiltrate noted on the CXR. She was started on i.v. ceftriaxone and azithromycin. Ultrasound guided throacentesis revealed fluid which was positive for malignant cells consistent with non-small cell carcinoma. CT scan showed a right hilar mass with extensive mediastinal lymphadenopathy and pleural nodularity and a nodule in the upper left lobe. Liver mets were confirmed. Seven days after the last treatment dose of the study drug was given the patient required a right-sided thoracostomy tube. The subject died 8 days later. It is the MO's assessment that this subject's death was attributable to her advanced metastatic lung disease.

AEs leading to discontinuing study drug

CAPSS-150

In the CAPSS-150 study, the applicant reported eighteen (7.0%) subjects who received levofloxacin 750 mg and twenty-two (8.3%) subjects who received levofloxacin 500 mg discontinued study treatment due to adverse events. According to the applicant, the most common events that led to discontinuation of the study medication were condition aggravated (three subjects), nausea (three subjects), vomiting (three subjects) and fever (two subjects) in the 750 mg group, and condition aggravated (five subjects), pleural effusion (three subjects), respiratory insufficiency (two subjects), cardiac arrest (two subjects) and rash (two subjects) in the 500 mg group (see **Appendix 6**).

CAPSS-171

In the CAPSS-171 study, the applicant reported seven (5.7%) subjects experienced adverse events that resulted in discontinuation of treatment. Of the ten adverse events that led to discontinuation of treatment, two were considered by the applicant to be related to the study drug: allergic reaction. Four adverse events were considered to be possibly related to the study drug: diarrhea and nightmares, worsened ankle pain and worsening liver enzymes. All other adverse events leading to discontinuation of study medication were considered not related or of doubtful relationship to the study medication. For those adverse events where outcome was known, all events resolved after discontinuation of levofloxacin. Outcome was unknown for two adverse events: insomnia and Herpes simplex. Allergic reaction was the only adverse event that occurred in more than one subject and led to discontinuation of the study medication (see **Appendix 7**).

QT Prolongation

There was no report of QT prolongation among the treatment subjects in the CAPSS-150 or CAPSS-171 study. After reviewing the reported adverse events for subjects receiving the study drug the MO concurs with the lack of findings that would indicate QT Prolongation.

Clinical Laboratory Evaluation

CAPSS-150

In the CAPSS-150 study one or more treatment-emergent markedly abnormal laboratory values was found in thirty (11.7%) subjects in the 750 mg group and thirty-three (12.5%) subjects in the 500 mg group). In > 4% of subjects from either treatment group no specific abnormalities were reported. The most common marked abnormalities in the 750 mg group were elevated glucose (3.6%) and elevated SGPT (3.6%); in the 500 mg group, decreased lymphocytes (3.1%) and decreased glucose (3.1%). The remaining abnormalities reported in the two treatment groups occurred at similar rates.

Appendix 8 summarizes the incidence of treatment-emergent markedly abnormal laboratory values in the 750 mg and 500 mg (comparator) groups.

Appendix 9 shows subject listing of treatment-emergent markedly abnormal laboratory values.

CAPSS-171

In the CAPSS-171 study statistically significant mean changes from baseline were observed for hematology (WBCs, neutrophils, lymphocytes, monocytes, eosoinophils, basophils and platelet count) and blood chemistry (sodium, glucose, creatinine, LDH, SGOT, total bilirubin and CrCl) parameters. Incidence of markedly abnormal laboratory values after initiation of study medication is shown in **Appendix 10**. **Appendix 11** shows subject listing of treatment emergent markedly abnormal laboratory values. Overall, 17 (13.8%) subjects had one or more markedly abnormal laboratory values. These included hematology parameters, in decreasing order of frequency, such as hemoglobin (6 subjects), decreased lymphocytes (4

subjects), and decreased neutrophils (1 subject). Among blood chemistry parameters, in decreasing order of frequency, markedly abnormal values included elevated BUN (three subjects), elevated SGPT (three subjects), decreased glucose (two subjects), elevated glucose (two subjects) and elevated creatinine (2 subjects). Subject 79004 had an abnormal hemoglobin value of 10.2 g/dL (normal range 11.5-15.8 g/dL) at posttherapy and subject 9003 had to discontinue the study medication due to worsening of liver enzymes.

Conclusions Regarding Safety Data

CAPSS-150

Treatment emergent adverse events observed in the CAPSS-150 and CAPSS-171 studies seemed consistent with the known safety profile of levofloxacin. In the CAPSS-150 study, the treatment of adults with mild to severe community acquired pneumonia with levofloxacin 750 mg q.d. for five days did not result in increased rates of treatment associated adverse events compared to the currently marketed levofloxacin regimen of 500 mg q.d. for 10 days. None of the deaths in either treatment group, 5/256 (1.9%) subjects in the levofloxacin 750 mg population and 9/265 (3.4%) subjects in the 500 mg population were attributable to the study medication. The majority of adverse events reported in either treatment group were mild or moderate in severity. In the 750 mg group eighteen subjects had at least one treatment-emergent adverse event of marked severity compared to twenty-eight subjects in the 500 mg group. Adverse events that were probably related to the study drug occurred in 18 (7.0%) subjects in the 750 mg group and 15 (5.7%) subjects in the 500 mg group. The most common events in the 750 mg group included nausea (5 subjects) and rash and condition aggravated (2 subjects each). The most common events in the 500 mg group included rash (3 subjects), insomnia, diarrhea, moniliasis and moniliasis genital (2 subjects each). There were no clinically significant changes in mean laboratory values from admission to post therapy in either treatment group. Markedly abnormal laboratory values due to the study drug occurred in similar proportions in subjects of the 750 mg group (11.7%) and the 500 mg group (12.5%).

CAPSS-171

In the CAPSS-171 study 59.3% of subjects reported at least one treatment emergent adverse event. The most common adverse events (in decreasing order of frequency) were insomnia, constipation, chest pain, headache, nausea, anxiety and pleural effusion. The events of chest pain and pleural effusion may be consequences of the community acquired pneumonia rather than related to the study medication. Five (4.1%) treatment subjects had drug-related adverse events which were considered mild or moderate in severity. Six subjects died during the CAPSS-171 study. None of the deaths were attributable to the study medication. Forty-five serious adverse events were reported in twenty (16.3%) subjects with only four (two allergic reactions, dehydration, diarrhea) of these AEs thought to be drug-related. Discontinuation of treatment occurred in seven (5.7%) subjects who had ten treatment related adverse events. Allergic reaction was the only drug related adverse event that resulted in discontinuation of the study medication. One or more markedly abnormal laboratory values were seen in seventeen subjects. Decreased hemoglobin was the only markedly abnormal laboratory value which occurred in > 5% of treatment subjects.

Conclusions and Recommendations

The applicant has adequately demonstrated that levofloxacin (Levaquin®), at a dose of 750 mg for 5 days, is safe and efficacious for the treatment of community acquired pneumonia due to S *pneumoniae, H influenzae, H parainfluenzae, M pneumoniae,* and C *pneumonia.* The medical officers' recommendation is for approval, with the caveat that the label should reflect the following:

- The efficacy of the 5-day regimen was not characterized for [redacted]
- Examination of outcome at a later time point 31-38 days post enrollment showed a trend to higher relapse rates in the 5-day treatment arm than the 10-day treatment arm (5% versus 1%).

It is also the medical officers' recommendation that the applicant be requested to agree to a Phase 4 commitment to investigate the reason for the lower efficacy observed in patients with renal impairment and subsequent dose modification.

Leonard Sacks, Medical officer DSPIDP.

Vicki Moncada, Medical officer DSPIDP.

CONCURRENCES:
HFD-590/TL ClinicalRRoca_____Signature_____Date

CC:
HFD-590/Original NDA # 20-634/S-028; NDA 20-635/S-027
HFD-590/Division File
HFD-590/MO/LSacks
HFD-590/MO/VMoncada
HFD-590/Stats/JZalkikar
HFD-590/StatsTL/KHiggins
HFD-590/Micro/SPeacock
HFD-590/MicroTL/SBala
HFD-590/Pharm/SHundley
HFD-590/Chem/Holbert
HFD-590/RPM/SPeacock

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Appendices

Appendix 1: Detailed efficacy review of individual trials

CAPS 150

Objective: To demonstrate that a 5 day course of levofloxacin (750mg IV or PO q.d.) was at least as effective as a 10 day course of levofloxacin (500mg IV or PO q.d.) in the treatment of "mild to severe" CAP.
Study design: A multi-center, randomized, double-blind, non-inferiority study

Study population
This was to include both hospitalized adult patients and outpatients. Residents of nursing homes for less than 14 days were also eligible.

Inclusion criteria

A diagnosis of mild to severe CAP was required based on the following criteria:

- Clinical signs and symptoms of a lower respiratory tract infection
  and
- Chest radiograph with acute infiltrate determined by a radiologist to be consistent with pneumonia, within 24 hours of study-drug administration
  and
- At least one of the following:
  Oral temperature ≥ 38° C or ≤35° C
  WBC>10,000/μl
  Bands<10%

Other inclusion criteria:

- Patients ≥18 years of age
- No prior antibiotic use
  or
  Prior antibiotic use of <24 hours' duration
  or
  Prior antibiotic use for ≥72 hours with two criteria for treatment failure:
  Persistent fever ≥100.8°F
  Worsening chest radiograph
  Increase in absolute neutrophil count by 20% or bands by 10%
  Respiratory rate>20 and faster than at initiation of therapy
  A new requirement for supplemental oxygen

  Comment: These criteria lack specificity for treatment failure; many are consistent with an erroneous diagnosis such as cardiac failure, recurrent pulmonary emboli, asthma on steroids etc. The reviewer ensured that these were a minority of patients in the database. Among the 528 enrollees, 34 (6%) had received more than 72 hours of prior antibiotics, 18 in the 5- day arm and 16 in the 10-day arm.
- Fine score ≤130 points (scores ≥70 required initial hospitalization for 24 hrs)
- Females of child bearing potential required a negative pregnancy test, and use of adequate contraceptive measures

Exclusion criteria

- Suspected resistant pathogen
- Previous failed therapy with a quinolone
- Quinolone allergy
- Life expectancy < 72 hours
- Hospitalization in the previous 2 weeks or month if antibiotics were given

- Probability of P aeruginosa- cystic fibrosis, bronchiectasis, lung abscess significant steroid use, mechanical ventilation
- Neutropenia <500 pmn/µl
- Creatinine clearance <50ml/min
- Empyema
- Aspiration pneumonia
- Moderate to severe pneumonia treated out of hospital
- HIV with CD4 <200
- Seizure disorders
- Inability to swallow tablets
- Pregnancy or nursing
- Expected need for other antibiotics or steroids
- Known or suspected meningitis

Comment: The inclusion criteria target a suitable population representative of community acquired pneumonia with radiographic confirmation. The extensive list of exclusions limits the determination of efficacy to a relatively healthy adult population with uncomplicated pneumonia where a favorable outcome is likely. For example those expected to die in 72 hours, those with suspected resistant pathogens, and those who might need other antibiotics or steroids are not included.

Study drugs

Table CAPPS 150-1: Treatment arms

5-day arm	10-day arm
Levaquin capsules 750mg Or Levaquin parenteral solution (500mg/vial)-1 ½ vials	Levaquin 500mg capsules Or Levaquin parenteral solution (500mg/vial)-1 vial
Patients received 5 days of antibiotic and 5 days of blinded placebo	Patients received 10 days of antibiotic

Capsules were overencapsulated and blinded
Infusions were constituted by the hospital pharmacist, aware of the patient's treatment allocation
Randomization was stratified by study center and by Fine risk classification (stratum I≤ 70 or stratum II, 70-130)

Concomitant medications
Non-study antimicrobials or steroids (>20mg prednisone or equivalent, per day) were prohibited. Use of Mg or Al based antacids was discouraged

Study visits

Table CAPSS 150-2: Timing of study visits

Visit 1	Day 1- admission
Visit 2	Day 3- on therapy
Visit 3	Day 12-16 –post therapy/early withdrawal
Visit 4	Day 17-21- post therapy
Visit 5	Day 31-38 – post study

Visit 1 included:

- a history and physical examination,

- chest x-ray,
- blood gas or pulse oximetry, serum chemistry and CBC
- sputum for gram stain and culture (aimed for samples with ≥25 polymorphonuclear leukocytes/low power field (LPF) and squamous cells <10/LPF)
- blood culture
- serology for M pneumoniae, L pneumophila and C pneumoniae
- Urine for L pneumophila antigen

Visit 2 (in person if possible though telephone contact permitted) included:
- Evaluation of signs, symptoms and adverse events
- Repeat sputum evaluation
- Repeat blood culture if initial positive
- Plasma for steady state levofloxacin blood levels at selected centers

Visit 3
- Similar to visit 1 (blood gas not performed, serology only if patient withdrawn)

Visit 4
- Similar to visit 1 (no chest x-ray, no serology)

Visit 5
- Similar to visit 1
- Convalescent serologies drawn (no serum chemistry, blood gas, CBC)

Early withdrawals were permitted for adverse events, renal insufficiency, clinical failure, death and other unforeseen reasons.

Evaluation of efficacy (at post-therapy and at post-study visits)

a) Clinical efficacy was subjectively determined by the investigator based on signs, symptoms and radiographic findings. Response was designated as:
- Cure- resolution of pre-treatment signs and symptoms with no need for further antibiotics for CAP
- Improvement-Incomplete resolution with no need for further antibiotics for CAP
- Failure- incomplete response or no response to therapy with the need for additional antimicrobials for CAP
- Unable to evaluate- due to loss to follow-up
- Relapse (at post study visit only) –improvement with subsequent deterioration

MO comment: The criteria for determination of failure are subjective and lack specificity. For example persistent cough, shortness of breath and radiological infiltrates may indicate underlying disease such as pulmonary edema, pulmonary embolus, carcinoma and COPD, rather than persistence of pneumonia.

b) Microbiological response by subject (at post-therapy and at post-study visits)
Microbiologic outcomes for patients with baseline pathogens were recorded as
- eradicated
- persisted
- unknown
- relapse (at post study visit only) –improvement with subsequent re-appearance of pathogen

Organisms considered to cause superinfection or colonization were not considered in the microbiological response.

Comment: The protocol does not identify the organisms regarded as colonizers. The reviewer will limit the evaluation of microbiological efficacy to traditional pneumonic pathogens seen in at least 10 patients.

c) Microbiological response by pathogen (at post-therapy)
For each admission pathogen, the possible outcomes were

- eradicated,
- presumed eradicated (in the absence of follow up culture but clinical cure),
- persisted,
- presumed persisted (in the absence of follow up culture but clinical failure),
- persisted with acquisition of resistance
- unknown

d) long term microbiological outcome (at post-study visit):

- Eradicated
- Microbiological relapse
- Presumed microbiological relapse
- Unknown

Pathogens identified on blood culture:
Criteria included two positive blood cultures, or one positive blood culture and one positive sputum culture. A single positive blood culture was sufficient in the case of *S pneumoniae.*

e) Microbiologic outcomes for bacteremia were listed as

- Eradicated
- Persisted
- Presumed persisted
- Persisted with acquisition of resistance
- Unknown

f) Evaluation of outcomes for pneumonia ascribed to atypical pathogens:
There were no microbiological criteria to determine a microbiological outcome.
The clinical outcome in these patients was determined as above.

Safety:
Treatment emergent adverse events were new events or aggravated events occurring up to 14 days after the last dose of active medication. The adverse events were graded according to severity and attributability.

Serious adverse events included those that were:

- fatal
- life threatening
- required or prolonged hospitalization
- caused significant or permanent disability
- congenital anomalies,
- deemed medically important

Statistical methods:
Types of analyses

1) Intent to treat- included all randomized subjects who took at least one dose of drug

2) Clinically evaluable-

- Clinical confirmed diagnosis with a consistent chest x ray within 24 hours of first dose

- Was evaluated at post-therapy (12-19 days and 7-14 days after last does of therapy in 5-day and 10-day arms respectively) or early withdrawal visits
- Received at least 3 days of therapy plus 1 additional dose in the 5-day arm and 4 additional doses in the 10-day arm.
- (Any clinical failure who had received at least 3 days of therapy was regarded as evaluable)

  Comment: Most patients with CAP will have an adequate clinical response within 3 days (ATS Am J Respir Crit Care Med, 2001; 163: 1730-1754) and patients showing ongoing deterioration during the first 2 to 3 days of therapy probably represent clinical failures. Even after 2 doses, some response would be anticipated.

  The reviewer identified 21 patients who received only 1 or 2 doses of study drug. The applicant recorded 14 as unevaluable, 4 in the 5-day arm and 10 in the 10-day arm. The reviewer accepted that this small number of subjects deemed unevaluable based on less than 3 days of therapy was too small to have a meaningful impact on the evaluation of drug efficacy.

- No more than 6 days of treatment in the 5-day arm and no more than 12 days of treatment in the 10-day arm.
- Did not receive concomitant effective antimicrobial therapy within 7 to 14 days of the test of cure visit
- (Any failure receiving concomitant effective antimicrobial therapy was evaluable)

3) Microbiologically evaluable:

- Required identification of a baseline pathogen on sputum or blood culture, or serology or urine antigen results indicating an atypical pathogen
- Appropriate cultures (<24 hours prior to start of therapy if prior antimicrobial use), cultures <24 hours after start of therapy
- Post therapy culture result had to be available (if sputum resolution occurred-bacteriological success was presumed, if subject was discontinued from study due to clinical failure, bacteriological failure was presumed).

Microbiologically unevaluabe:

- No bacteriological confirmation
- Loss to follow up
- Deviation from protocol regimen
- Effective concomitant therapy
- Inappropriate culture
- Other protocol violation

Case definitions for atypical pathogens:

2) Chlamydia pneumoniae

Respiratory signs and symptoms compatible with pneumonia plus:

A four fold increase or decrease in the immunoflourescence titer (IgG or IgM) at visit 3 or visit 5.

or

Positive culture for chlamydia pneumoniae

3) Mycoplasma pneumoniae

Clinical and radiological evidence of pneumonia plus:
Single IgM ELISA > 1:16 or a fourfold increase or decrease at visit 3 and 5
or
Single IgG ELISA > 1:128 or a fourfold increase or decrease at visit 3 and 5

Comment: The diagnostic criteria for these atypical pathogens are not validated and vary in stringency. Cases of atypical pneumonia will be individually evaluated, with emphasis on culture or antigen isolation as the best level of evidence, fourfold changes in titer as the next best level of evidence and single positive titers as the poorest level of evidence.

Efficacy analysis:
The applicant elected to evaluate clinical efficacy at the post-therapy visit as the primary response. This was to be assessed 7-14 days after the last dose of active medication.

FDA had requested that primary efficacy be assessed the same interval after initiation of therapy in both arms; in practice, at visit 4 for all patients. This was to allow both arms equal periods for resolution of signs and symptoms, to allow for the detection of relapses in the short course arm due to inadequate therapy and in practice, to allow for an equitable and clinically meaningful comparison of two regimens. The applicant provided this as a secondary analysis.

Outcomes were classified as cure, improvement, failure and unable-to-evaluate. Cure and improvement were also analyzed together as "successes".
The difference in "success" rates was calculated (10 day – 5 day). The upper bound of the 95% confidence interval around this difference was not to exceed 15% for success rates between 80 and 90% and not to exceed 10% for success rates >90% in either of the groups.

The clinical response at the post-study visit was to be summarized using as the denominator, the number of subjects cured or improved during the 7 – 14 day post therapy time window, who returned poststudy.

None of the planned pharmacokinetic studies in this protocol were performed.
Protocol changes:
Numerous protocol changes were made in an amendment on May 15 2001. These included

- Changes is samples size,
- permission to treat as outpatients at investigator's discretion,
- changing logistics of assigning randomization numbers,
- providing for sputum and urine L pneumophila testing at admission,
- deleting the requirement for a baseline PO2,
- deleting requirement for repeat serology testing in early withdrawals,
  Comment: This would reduce the number of patients that could be confirmed to be infected with a baseline pathogen
- replacing the legionella ELISA with the "Wampole test"
  Comment:The applicant cites a "discrepancy with the negative control in the in house ELISA motivating re-testing of all samples using the Wampole ELISA for IgG and IgM. The diagnosis was regarded as positive if the initial test was negative and any subsequent test was positive. Without criteria for a minimum titer change the reviewer doubts the validity of this criterion. This is addressed in the reviewer's evaluation of the diagnosis of legionella in the microbiologically evaluable population.

- Allowing up to 48 hours post initiation to obtain a chest x ray

If a subject in the 5-day arm had 2 post therapy visits within the 7-14 days following initiation of therapy, the later of the two visits was to be used to assess outcome. The applicant then states that this was not done in the following two cases:

Subject 71009: A patient in the 750mg group entering with fever shortness of breath cough, pleuritic pain and rales with a left lower lob infiltrate in chest X ray. 7 days after initiation of therapy the patient had

improved. However the signs and symptoms and new radiological changes in the right lung were found on day 13. The investigator assessed this as improved at visit 3 and a failure at visit 4.

Subject 91012: A patient in the 750mg group entering with fever, chills, shortness of breath cough, pleuritic pain and rales with a left lower lobe infiltrate on chest X ray. Eight days after initiation of therapy the patient's signs and symptoms had disappeared. However the signs and symptoms and new radiological changes in the right lung were found on day 14 in addition to a small, left lower lobe infiltrate. The applicant assessed this as a success at visit 3 and a failure at visit 4.

Comment: The reviewer regards the above two cases as evidence of inadequate initial therapy and considers them both technically as failures at visit 4. However, pathologically these 2 cases may represent relapses due to inadequate therapy since both improved at visit 3 and then deteriorated after stopping therapy.

Results:

Study centers: 70 (all in USA)
Total patients enrolled: 530

The following 3 tables summarize the composition of the applicant's populations for analysis, the primary reasons for exclusion of patients and the demographic characteristics of the study population..

Table CAPSS 150-3: Composition of applicant's populations for analysis

	5 day	10 day		5 day	10 day
Randomized	257	273			
			Did not take medication	1	1
ITT	256	272			
			Excluded from safety		7
Safety	256	265			
			Clinically unevaluable	58	73
Clinically evaluable	198	192			
			Microbiologically unevaluable	95	100
Microbiologically evaluable	103	92			

Table CAPSS 150-4: (From Applicant's Table 7.2) Primary reasons for clinical non-evaluability at visit 4

	5-day	10-day
Unconfirmed clinical diagnosis	8	12
Lost to follow up	3	5
Deviation from dosing regimen	14	26
Effective concomitant therapy	3	4
Inappropriate posttherapy evaluation date	26	24
Other protocol violation	9	9
Total	63	80

Table CAPSS 150-5: Demographics (ITT population) listed as %

	5 day regimen (n=256)	10 day regimen (n=272)
Female	42	40
Race		
Caucasian	70	67
Black	20	24
Asian	2	1
Hispanic	7	8

	5 day regimen (n=256)	10 day regimen (n=272)
Other	1	<1
Age		
<=45	37	31
46-64	32	33
>=65	31	36
Fine score		
I/II (milder)	61	55
III/IV (more severe)	40	45

Comment: The two study arms were demographically similar. According to the Fine scores, the patients in the 10-day arm were somewhat sicker. Similar demographic characteristics were found with the clinically evaluable population.

Symptom scores in both groups were similar. Cough was present in 92%, shortness of breath in 80%, fever, chills and purulent sputum in >69%. Smoking history was similar in the two arms. Approximately 1/3 of the patients never smoked. A history of alcoholism (not defined) was absent in 85% of study participants.

The reasons for premature withdrawal from study medication are shown below.

Table CAPSS 150-6: ITT withdrawals:

	5-day	10-day
At entry	256	272
Stopped study medication early	34	48
Adverse event	16	21
Renal insufficiency	0	1
Subject choice	3	4
Clinical failure	3	2
Other	12	20
Lost to follow up	3	6

Comment: There were significantly more early withdrawals in the 10-day arm where the treatment duration was double the 5-day arm. Only a small number of these withdrawals were for adverse events.

Protocol deviations potentially affecting the evaluation of efficacy (concomitant antimicrobials, violations in duration of therapy, other)

Table CAPSS 150-7: Concomitant antimicrobial therapy (Patient numbers in parentheses)

	Prior to post-therapy (visit 4)	Between post-therapy visit (visit 4) and post-study
5 day	3	10
10 day	4	5

The applicant regarded the 7 patients treated with antimicrobials before visit 4 (who were not failures) as unevaluable. The reviewer concurred with this assessment.

As described below, the reviewer evaluated those treated with antimicrobials between visit 4 and the post study visit to determine whether a recurrence of pneumonia was the reason for reinitiating antimicrobial therapy.

The following summary was compiled from the case report forms of patients who received concomitant antimicrobials between visit 4 (post therapy) and visit 5 post-study. The reviewer was concerned that some patients requiring antibiotics after completing therapy for pneumonia might represent relapses of infection

where treatment was inadequate. Ten patients in the 5-day arm and 5 in the 10-day arm received antimicrobials following completion of study therapy. In 3 of these subjects (all in the 5 day arm), the reason for receiving additional antibiotics was "pneumonia".

Table CAPSS 150-8: Patient who received additional antibiotics after the treatment period

Subject number	antimicrobial	Study day	Indication
5 day arm			
4001	Amoxi/clav, levaquin	21-27	L otitis media
*10010	Levaquin, genta	29- 36	pneumonia
15007	Zithromax, rocephin	21-24	"prophylaxis"
15014	Tequin	12-14	"general prophylaxis"
*22006	Augmentin	14-21	Pneumonia and sinus pressure (recorded failure at visit 3)
61005	Amoxi/clav	23-28	dental abscess
78025	Zithromax	21-29	"prophylaxis due to cold"
78026	Keflex	10-24	Cellulitis
134005	Cipro	21-22	"prophylactic, possible bladder infection"
*134007	Doxycycline	7-16	pneumonia. Recorded as long term cure
10 day arm			
6018	Avelox	24-28	Pharyngitis
7002	Keflex	-1-7	sores on legs
35001	Doxycycline	19-?	"prophylaxis bronchitis"
39001	Augmentin	20-29	sore throat
133010	Zithromax	29-34	"URI"

* the reviewer regards these three cases as clinical relapses

Duration of treatment:

In the 5 day arm, five subjects received therapy for >6 days- 9006, 13002 23005, 47025 106002

Table CAPSS 150-9: Duration of therapy

Days of therapy	.	1	2	3	4	5	6	7	8	9	10	11+
5 day regimen	3	6	2	11	8	221	4	1				
10 day regimen	6	12	10	8	3	4	3	2	5	5	211	3

Comment: There were relatively few significant departures from the prescribed duration of therapy. Only 5 subjects received more than 5 days of therapy in the short course arm. The reviewer regarded both arms as representative of the respectively proposed durations of therapy.

The use of oral or intravenous therapy is described below.

Table CAPSS 150-10: IV or oral treatment on day 1 (from SMED)

	IV	Oral
5 day arm	108	155
10 day arm	127	151

Comment: There was more use of intravenous therapy in the 10-day arm, possibly due to a higher prevalence of more severe disease in this group.

Violation of entry criteria

The reviewer was concerned that the ITT population identified above did not accurately represent patients with community acquired pneumonia of bacterial etiology, in order to determine the drawbacks or advantages of short course therapy. Specifically, it appeared that the inclusion criteria quoted below were not satisfied in many or the enrolled patients:

A diagnosis of mild to severe CAP was required based on the following criteria:
Clinical signs and symptoms of a lower respiratory tract infection
and
Chest radiograph with acute infiltrate determined by a radiologist to be consistent with pneumonia, within 24 hours of study-drug administration
and
At least one of the following:

Oral temperature ≥ 38° C or ≤35° C
WBC>10,000/μl
Bands<10%

Comment: The reviewer elected to focus the efficacy determination on patients who satisfied the inclusion criteria with at least a consistent chest X ray and a documented fever (or hypothermia) or abnormal white blood cell count.

Patients were included with normal chest radiographs:
From file "XRAY", admission films were reviewed for acute infiltrate [field acute, 1=no 2=yes]. Of the admission films on 528 unduplicated subjects, 16 had no acute infiltrate and 1 had a missing radiological description.

Table CAPSS 150-11: Patients with admission X rays not recorded as showing "acute infiltrate"

Subject number	Radiological description	Treatment arm 1=5-day, 2=10-day	Description from CRF
1001*		1	"Dx Pyelonephritis, pneumonia rule out"
3008*	HYPERLUCENCY WITH FLUID IN THE MINOR FISSURE	2	
6023*		2	
27007* (absent reading)		2	
37005*	LUNGS FREE OF INFILTRATE, NORMAL CHEST	1	
37007*	THERE IS A PULMONARY DENSITY NOT SYNONYMOUS WITH INFILTRATE.	1	
47027*	NO CONFLUENT AIR SPACE DISEA SE SEEN.	2	
50001	LEFT LOWER LOBE OPACITY, CONSISTENT WITH EARLY PNEUMONIA.	2	
55002*	HILAR BRONCHIAL THICKENING	2	
72004*	LINEAR OPACITY AT LEFT BASE WHICH MAY REPRESENT AIRSPACE	2	

Subject number	Radiological description	Treatment arm 1=5-day, 2=10-day	Description from CRF
	DISEASE LIKELY ATELECTASIS OR SCARRING		
87001*		1	
91016*	R) APEX SCARRING, RUL CHAIN SUTURES, HYPEREXPANSION OF LUNG FIELDS, (B) LUNG PLEURO PARENCHYMAL SCARRING, ATHEREMATOUS CHANGES OF THORACIC AORTA	2	
105001*		2	
108004*		1	
108007*		1	
110002*		2	
129002*	CALCIFIED GRANULOMA RIGHT LOWER LOBE. CHRONIC OBSTRUCTIVE PULMONARY DISEASE	2	

*excluded from reviewer's clinically evaluable population

Patients were included with normal white blood cell counts and normal temperatures:

Table CAPSS 150-12: Temperature on admission: (from VITALS)

	Hypothermic (<36 C)	Afebrile 36-38 C	Febrile (>38 C)
5 day arm C	5/256	127/256 (49.6%)	124/256
10 day arm C	10/272	143/272 (52.5%)	119/272

The applicant stated that subjects "who had a fever but were afebrile at admission due to antipyretic medication were allowed into the study." The reviewer did not find documentation of prior fever or of antipyretic medication at the time the admission temperature was recorded.

Table CAPSS 150-13: WBC on admission (from SLAB)

	<3.8	3.8-10.7	>10.7
5 day arm	3/236	108/236 (45.7%)	125/236
10 day arm	1/250	108/250 (43.2%)	141/250

There were 11 patients with >10% bands. All also had abnormal WBC counts.

Altogether there were 104 patients with normal temp (>35° C and <38°C), normal WBC (>3.8 and <10.7) and bands <10% at the admission visit. Of these, 102 were excluded from the reviewer's clinically evaluable population. Two patients were afebrile at enrolment but febrile on therapy and the reviewer accepted these 2 as clinically evaluable.

Other protocol violations

Table CAPPS 150-14: Applicant's reasons for clinical and microbiological unevaluablity at post therapy (visit 4)

	Clinically unevaluable		Microbiologically unevaluable	
	5-day	10-day	5-day	10-day
Unconfirmed clinical diagnosis	8	12	8	12
Unconfirmed microbiological			123	139

diagnosis				
Inappropriate culture			11	11
Lost to follow-up	3	5	2	1
Deviation from dosing regimen	14	26	8	10
Effective concomitant therapy	3	4	0	1
Inappropriate evaluation date	26	24		
Other violations	9	9	6	6
Total unevaluable	63	80	158	180

Comment:
Exclusions based on deviations from the dosing regimen were almost twice as frequent in the 10 day arm, where compliance with 80% of the regimen was more demanding than in the 5 day arm. Patients being seen outside the limits of the test-of cure visit were the most common reasons for exclusion from those who were clinically evaluable. This occurred equally across the arms. Lack of microbiological confirmation was the most common reason that patients could not be microbiologically evaluated.
Exclusions from evaluability were frequent in this study, but apart from reducing the numeric power of the study, they were not considered by the reviewer to bias the evaluation of efficacy.

Nine subjects received the treatment allocated to the opposite treatment arm. These subjects were analyzed according to the treatment they received. These and other protocol deviations are tabulated below.

Table CAPSS 150-15: Other protocol deviations

Protocol violation	Number of subjects	Applicant's analysis	FDA comment
Wrong treatment allocation	9	Analyzed according to treatment received	Concur
Received <80% or >120% of prescribed medication	10	Excluded from clinically evaluable population	Concur
Received non-study antimicrobials between admission and test-of-cure	9	Excluded from clinically evaluable population	Concur
Telephone assessment only for visit 3 and/or 4	5	Excluded from clinically evaluable population	Concur

Efficacy evaluation:
Disease severity was categorized as:
Milder- Fine class I/II (Fine score ≤70)
More severe - Fine class III/IV (Fine score >70 and ≤ 130)

Table CAPSS 150-16: Distribution of "fine scores" for applicant's analyses. In each population, the proportion of patients with more severe disease (Fine class III/IV) is listed.

	ITT	Safety	Clinically evaluable	Microbiologically evaluable
5-day	101/256 (39%)	101/256 (39%)	76/198 (38%)	36/103 (35%)
10-day	123/272 (45%)	121/265 (46%)	86/192 (45%)	33/92 (36%)

Comment: The patients in the 10-day arm had more severe illness than those in the 5-day arm. This potentially weakens the conclusions on the efficacy of the 5-day arm. A stratification of response rates by disease severity will be performed.

ITT population:
In view of the large numbers of patients enrolled despite normal temperatures and white blood cell counts, the reviewer regarded the ITT population as a poor representation of CAP. The applicant reported clinical success rates in this ITT population of 87.5% in the 5- day arm and 81.3% in the 10-day arm (95% CI for

the difference –12.6 to 0.1). The reviewer relied on the clinically evaluable population (see below) for the primary determination of comparative drug efficacy.

Clinically evaluable population:

Composition of reviewer's clinically evaluable population:
This included the patients in the applicant's clinically evaluable population except:

- 16 patients with a normal admission chest Xray
- 102 patients with a normal temperature (Temp >35° C and <38° C at admission), and normal WBC (>3.8 and <10.7) and bands <10% at the admission visit. (Two patients who were afebrile at enrollment but febrile on treatment were included by the reviewer among the clinically evaluable population.)

This resulted in excluding 115 unduplicated patients from the Applicant's ITT population.
A further 95 patients were determined by the applicant to be unevaluable for other reasons described above.
The reviewer agreed with this assessment.
The population regarded as clinically evaluable by the reviewer is shown below.

Table CAPSS 150-17: Derivation of FDA clinically evaluable population

ITT total	528
Excluded because of normal temperature, white blood count or chest X ray	115
Excluded by applicant as clinically unevaluable	95
Clinically evaluable population (FDA)	318

Clinical evaluation in the "FDA clinically evaluable population" is described below for each study visit.

Table CAPPS 150-18: FDA analysis of clinical efficacy (clinically evaluable population)

	5 day n=164	10 day n=154
Visit 3*		
No record	2	1
Cure	99 (61%)	82 (54%)
Improved	53 (38%)	60 (39%)
Failure	10 (6%)	11 (7%)
Uneval	0	0
Visit 4*		
No record	5	0
Cured	122 (77%)	110 (71%)
Improved	24 (15%)	31 (20%)
Failure	13 (8%)	13 (8%)
Post study*		
No record	5	4
Unable to eval	8	3
Cured	119 (79%)	123 (84%)
Improved	12 (8%)	9 (6%)
Failure	13 (9%)	13 (9%)
Relapse	7_1 (5%)	2 (1%)

*percentages of evaluable patients at each visit
$_1$ Includes two patients identified by the applicant as unevaluable but by the reviewer as relapses since they required additional antibiotic treatment after completing the study drug for "pneumonia"

For visit 4 and post-study outcome, all failures at visit 3 were carried through.

MO comment:

- *There were significantly more patients lost to follow up or unevaluable in the 10-day arm than the 5-day arm at all study visits. The reason is not clear although adverse events did not appear to account for the difference.*
- *Success rates were similar for the two arms at all 3 visits*
- *Documented relapse rates were higher in the 5-day arm*

Table CAPSS 150-19: Applicant's evaluation of clinical efficacy 7-14 days post therapy (clinically evaluable population)

	5 day	10 day
Visit 3*		
Evaluable	198	
Cure	131 (66.2%)	
Improved	52 (26.3%)	
Failure	15 (7.6%)	
Visit 4*		
Evaluable		192
Cured		138 (71.9%)
Improved		37 (19.3%)
Failure		17 (8.9%)
Post study*		
Evaluable	172	170
Improved	157 (91.3%)	164 (96.5%)
Relapse	7 (4.1%)	2 (1.2%)
Unevaluable	8	4

*percentages of evaluable patients at each visit.

At the post-study visit, the applicant evaluated only those patients who were cured or improved at the post-therapy visit.

Comment: The applicant chose to analyze the clinical response 7-14 days after completion of therapy, allowing less time for resolution in the 5-day arm. The reviewer considers this the likely reason for inferior cure rates in the 5-day arm. When FDA performed the efficacy analysis on the population identified by the reviewer as evaluable, and responses were compared at visit 4 for both arms (17-24 days after study enrolment), overall cure rates were higher in the 5-day arm.

Table CAPSS 150-20: FDA analysis of clinical success (clinically evaluable population)
[Success = cure + improved
Failure = failures (+ relapses in the case of the post-study visit)
N= success + failure (absent data or unable to evaluate were excluded)]

	Visit 3	Visit 4	Poststudy
5-day			
N (evaluable)	162	159	151
Success	152 (94%)	146 (92%)	131 (87%)
10-day			
N (evaluable)	153	154	147
Success	142 (93%)	141 (92%)	132 (90%
95% confidence interval (10- day minus 5-day)			
	-7% to 5 %	-6.4% to 5.9%	-4.9% to 11%

Table 29: Applicant's analysis of clinical success (clinically evaluable population)

	Visit 3	Visit 4	Poststudy
5-day			
N (evaluable)	198		
Success	183 (92.4%)		
10-day			

N (evaluable)		192	
Success		175 (91.1%)	

MO comment: In the reviewer's independent analysis of the study population, patients were only included that fully satisfied the protocol requirements for the diagnosis of CAP. The results obtained were similar to those reported by the applicant. Statistical comparison of success rates at visit 4 confirmed equivalence of the regimens for this primary endpoint, with an upper limit of the 95% confidence interval of the difference being 5.9%.
Relapses however were more common in the 5- day regimen.

Failures that occurred before completing the assigned duration of therapy (early withdrawals) would not indicate a failure due to inadequate treatment duration. The reviewer examined all failures in the FDA clinically evaluable population to determine comparative failure rates for individuals who completed therapy.

Table CAPPS 150-21: Early withdrawals among the 28 clinical failures at visit 4

	5 day arm	10 day arm
Early withdrawal	7	5
Completed regimen	8	8
% of evaluable patients at visit 4 who failed after completing therapy	8/159 (5%)	8/154 (5%)

Comment: There were no significant differences in the failure rates for the two arms among patients who completed their respective courses of therapy.

Subgroup analysis by severity of disease:
Disease severity was categorized as:

- Milder- Fine class I/II (Fine score ≤70)
- More severe - Fine class III/IV (Fine score >70 and ≤ 130)

Table CAPPS 150-22: Outcome by severity of disease in the clinically evaluable population

Milder disease			**More severe disease**		
	5 day n=103	10 day n=82		5 day n=61	10 day n=72
Visit 3			**Visit 3**		
Unevaluable	1	0	Unevaluable	1	1
Cure	62 (61%)	45 (55%)	Cure	37 (62%)	37 (52%)
Improved	33(32%)	34 (41%)	Improved	20 (33%)	26 (37%)
Failure	7(7%)	3 (4%)	Failure	3 (5%)	8 (11%)
Visit 4			**Visit 4**		
Unevaluable	5	0	Unevaluable	0	0
Cured	78 (80%)	61 (74%)	Cured	44 (72%)	49 (68%)
Improved	12 (12%)	17 (21%)	Improved	12 (20%)	14 (19%)
Failure	8 (8%)	4 (5%)	Failure	5 (8%)	9 (13%)
Post study			**Post study**		
Missing	5	3	Missing	0	1
unevaluable	4	2	unevaluable	4	1
Cured	75 (80%)	66 (86%)	Cured	44 (77%)	57 (81%)
Improved	8 (9%)	6 (8%)	Improved	4 (7%)	3 (4%)
Failure	8 (9%)	4 (5%)	Failure	5 (9%)	9 (13%)
Relapse	3 (3%)	1 (1%)	Relapse	4 (7%)	1 (1%)

Comment:

- *Failure rates were similar for patients with mild and with more severe disease in the 5-day arm, but failure rates were higher for patients with more severe disease in the 10-day arm.*
- *There was no significant difference in success rates for the two arms when evaluated by severity of diseases although relapses appeared more frequent in the short course arm regardless of disease severity.*

Deaths:

There were 14 deaths in study patients, 9 in the 10 day arm and 5 in the 5-day arm.

Table CAPSS 150-23: Deaths in study patients

Patient number	]	of death	cause	Treatment arm
6027			Myocardial infarct	5-day
38018			Respiratory insufficiency	5-day
71001			Myocardial infarct	5-day
79008			COPD/sepsis	5-day
91015			Bronchietasis/respiratory insufficiency	5-day
3003			Angina/LVF/ Resp depression	10-day
12001			Condition aggravated	10-day
15011			Cardiac arrest, respiratory insufficiency	10-day
37006			Arterial thombosis (leg)	10-day
37014			Myocardial infarction	10-day
38003			Atrial fibrillation, respiratory insufficiency	10-day
57002			Endocarditis, multiple organ failure, mitral insufficiency	10-day
99002			Multiple organ failure	10-day
134014			Respiratory insufficiency	10-day

MO comme All deaths in the 5-day arm occurred long after completion of therapy and are unlikely to .. e resulted from treatment failure. Numerically the mortality was lower in the 5-day arm.

Characterization of microbiological etiology

From the all pathogens identified on admission, the reviewer excluded a total of 83 pathogens since these cases were found to have a normal white blood count and temperature, or normal chest Xray on admission. The excluded pathogens and populations for microbiological analysis are detailed below.

Table CAPSS 150-24: Distribution of pathogens in FDA population

	Total number of isolates	**% isolates excluded by reviewer**
Typical pathogens		
S pneumoniae	67	18%
H influenzae	34	20%
H parainfluenzae	26	19%
S aureus	9	22%
P aeruginosa	7	0

	Total number of isolates	% isolates excluded by reviewer
E cloacae	7	0
M catarrhalis	6	16%
E coli	5	40%
K pneumoniae	4	25%
S agalactae	4	25%
Atypical pathogens		
M pneumoniae	99	26%
C pneumoniae	46	14%
Legionella pneumophila	19	3%

MO comment: The principal pathogens in this cohort were Mycoplasma pneumoniae, S pneumoniae, Chlamydia pneumoniae, H influenzae, H parainfluenzae, and Approximately 1/5 pathogens were excluded because of a normal temperature and white cell count or normal chest Xray. Among those organisms with >10 representative isolates, the exclusion rate was somewhat higher for mycoplasma.

The reviewer compared the distribution of pathogens in this study with the distribution of pathogens reported from the literature of pneumonia studies, (as summarized in the tables below), and concluded that they were similar.

In various published studies the following estimates of etiology in outpatients with CAP have been made (Am J Respir Care med 2001;163:1730-1754).

Etiology	*Incidence*
No pathogen	*40-50%*
Viral infections	*36%*
Mycoplasma pneumoniae	*13-37% (Concurrent bacterial infection may occur)*
S pneumoniae	*9-20%*
Chlamydia pneumoniae	*17%*
Legionella species	*0.7-13%*

In hospitalized, non-ICU patients with CAP, the published spectrum of pathogens differs as shown below (Am J Respir Care med 2001;163:1730-1754)

Etiology	*Incidence*
No pathogen	*20-70%*
S pneumoniae	*20-60%*
H influenzae	*3-10%*
S aureus, enteric gram negatives, atypical pathogens	*≤10%*

Efficacy versus typical pneumonic pathogens:

High eradication rates were demonstrated for individual pathogens although the representative numbers of patients were small.

Table CAPSS 150-25: Eradication rates by pathogen (FDA)

	5-day arm		10-day arm	
Typical pathogens	Eradication rate	unknown	Eradication rate	unknown
S pneumoniae	19/20	4	16/20	5
H influenzae	9/9	0	10/12	2
H parainfluenzae	9/9	0	8/9	1

Efficacy versus atypical pneumonic pathogens:

The applicant's diagnosis of atypical pneumonia was based on several possible serological criteria. (See case definitions for atypical pneumonia, page 15.) The reviewer evaluated the cases reported as "atypical pneumonia" with emphasis on culture or antigen isolation as the best level of evidence, fourfold changes in titer as the next best level of evidence and single positive titers as the poorest level of evidence.

Table CAPSS 150-26: Analysis of the serological evidence supporting the diagnosis of atypical pneumonia (FDA) Clinical success rates are shown for each diagnostic category.

Pathogen	750 mg, 5-day	500 mg, 10-day
Chlamydia pneumoniae IgG (fourfold increase/decrease in titer at Visit3 and 5)	12/12	6/6
Chlamydia pneumoniae IgM (Fourfold increase/decrease in titer at Visit 3 and 5)	7/9	1/2
Total (minus MO exclusions, Microbiological exclusions and duplicates.)	13/15	6/6
Mycoplasma pneumoniae IgG Single > 1:128 Titer Fourfold increase/decrease at visit 3 and 5	21/21 7/7 14/14	19/20 7/7 12/13
Mycoplasma pneumoniae IgM Single >1:16 titer fourfold increase/decrease at visit 3 and 5	10/11 7/8 3/3	6/7 1/2 5/5
(Minus MO exclusions, Microbiological exclusions and duplicates.)	27	26

MO Comment:
All 21cases of C pneumoniae infection were diagnosed on the basis of a 4 fold titer change from baseline and the clinical success rates were >86%.
Of the 53 patients with positive mycoplasma serological tests, 27 were confirmed with a fourfold titer change in IgG and 8 with a fourfold titer change for IgM. Among these, success rates were 100% in the 5-day arm.
Only 9 cases of [illegible] were confirmed either by a fourfold titer change, culture or antigen identification, 2 of which were in the 5-day arm.
The data are sufficient to support efficacy for mycoplasma and Chlamydia but not fc

The applicant reported the clinical and the microbiological outcome at visit 4 for both arms. The results for the principle pathogens (10 or more isolates) are shown below.

Table CAPSS 150-27: Eradication rates by pathogen (applicant) [from table 19.2 p142]

	5 day arm	10 day arm
S pneumoniae	19/22 (86.4%)	17/20 (85%)
H influenzae	9/10 (90%)	12/14 (85.7%)
H parainfluenzae	12/12 (100%)	9/10 (90%)
Mycoplasma	38/40 (95%)	34/36 (94.4%)
Chlamydia	19/21 (90.5%)	16/16 (100%)

MO comment: microbiological eradication rates in both treatment arms were similar for the organisms most frequently identified, both in the applicant's anlaysis and in the FDA analysis.

Clinical and microbiological response rates were similar as shown below.

Table CAPSS 150-28: Clinical and Microbiologic Response for the Pathogen of Primary Interest (FDA analysis)

Pathogen	Levofloxacin 750 mg q.d.				Levofloxacin 500 mg q.d.			
	Clinical Outcome (cure + improved)		Microbiologic Outcome (eradicated)		Clinical Outcome (cure + improved)		Microbiologic Outcome (eradicated)	
	n	(%)	n	(%)	n	(%)	n	(%)
Typical Pathogens								
Haemophilus influenzae	12/12	(100)	12/12	(100)	11/12	(92)	10/12	(83)
Haemophilus parainfluenzae	10/10	(100)	10/10	(100)	8/9	(89)	8/9	(89)
Streptococcus pneumoniae	19/20	(95)	19/20	(95)	18/20	(90)	16/20	(80)
Atypical Pathogens								
Chlamydia pneumoniae	13/15	(87)	13/15	(87)	6/6	(100)	6/6	(100)
Mycoplasma pneumoniae	26/27	(96)	26/27	(96)	24/26	(92)	24/26	(92)

MO Comment:
- *There were no substantial differences between the arms in the outcome for each organism. The clinical success rates and microbiological eradication rates were high in all cases*
- *The rates listed above for atypical pathogens excluded cases where the diagnosis was based on a single positive serology titer. Hence the number of cases is lower than the number of cases reported by the applicant below.*

Clinical cure and success rates were reported by the applicant for the principal pathogens.

Table CAPSS 150-29: Applicant reported clinical outcomes in microbiologically evaluable patients (Table 13.2)

		5 -day	10-day
S pneumoniae	N	23	23
	Clinical Cure	69.6%	87%
	Clinical Success	82.6%	91.3%
H influenzae	N	10	14
	Cure	80%	78.6%
	Success	90%	92.9%
H parainfluenzae	N	12	10
	Cure	75%	80%
	Success	100%	90%
Mycoplasma	N	40	36
	Cure	72.5%	72.2%
	Success	95%	94.4%
Chlamydia	N	21	16
	Cure	66.7%	75%
	Success	90.5%	100%

MO comment:
The reviewer accepted success rates as representative of the response. By definition "Cure" required complete resolution of signs and symptoms and "improvement" required improvement of signs and symptoms. Without the need for further antibiotics, both "cure" and "improvement" reflected clinical success.

- *In the applicant's analysis, cure rates were inferior for S pneumoniae in the short course arm though absolute numbers were small. The reviewer investigated the failures among patients with S pneumonia to better understand the difference between the arms. This analysis is provided below.*
- *The reviewer questions the etiological significance of H parainfluenzae.*

Reviewer's summary of the 6 subjects with *S pneumoniae* who failed at visit 4:
27006 (5-day arm) DOB 1962, white female, Fine score 48, nasopharyngial swab - *S pneumoniae.*
On day 3 no microbiological growth but febrile (100.9F) and withdrawn, Pleural effusion documented at visit 3. [This would not indicate a failure of the duration of therapy.]

61001 (10-day arm) DOB 1922, white male, diabetes, heart disease, nasopharyngeal swab -*S pneumoniae*, improved at day 3.
At visit 3, investigator recorded worsening of RUL pneumonia, although patient was afebrile.

78024 (5 day arm) DOB 1950, white female, blood culture *S pneumoniae.*
At visit 3, temperature 100.8F, small L pleural effusion recorded.

79006 (10 day arm) DOB 1957 white male, temp 100.7, dense bilateral pneumo nia, blood culture *S pneumoniae.*
At visit 3 temperature 98.1F, worsening of bilateral infiltrates, patient was intubated, blood culture still positive for *S pneumoniae*

91012 (5 day arm) DOB 1929, white male, temperature 101.8F, Fine score 111, sputum positive *for S pneumoniae*. At visit 3, investigator recorded clinical cure.
At visit 4: Temperature 99.1F, new RUL infiltrate, sputum positive for *S pneumoniae*

91017 (5 day arm) DOB 1921 black male, Fine score 80.

At visit 3, persistent cough, purulent sputum and chest pain, afebrile, sputum culture negative for *S pneumoniae*

MO comment: The reviewer considered cases 79006 and 91012 as most compelling for antimicrobial failure. There was no clear indication that antimicrobial failure was more frequent in the 5-day arm for patients with S pneumoniae infection.

Blood cultures:
There were 18 patients in the study with positive blood cultures on admission. Most were infected with *S pneumoniae*. The outcome for each of these patients is described in the table below.

Table CPASS 150-30: Outcome among patients with positive blood cultures

	5-day arm	10-day arm
S pneumoniae		
Unable to evaluate	0	2
Cured	4	4
failed	3	1

blood cultures for S pneumoniae on admission. Owing to the very small number of patients with positive blood cultures, this result in inconclusive.

Relapses:

The following subjects were identified with clinical relapses at the post-study visit, 31 to 38 days after the start of therapy in both arms.

Table CAPSS 150-31: Relapses at post-study

Study number	Treatment arm	Fine score	Organism	Outcome at visit 4	Clin Evaluable (FDA)
3005_1	5 day	97	-	Improved	No
10006_1	5 day	46	-	Improved	No
10010	5 day	120	-	Improved	Yes
22005	10 day	59	*S pneumoniae/ M catarrhalis*	Cured	Yes
79004	10 day	77	*H influenzae/* Mycoplasma	Improved	Yes
79008	5 day	96	-	Improved	Yes
89002	5 day	36	Mycoplasma	cured	Yes
94002	5 day	55	-	improved	Yes
99001	5 day	75	-	cured	Yes
134007_2	5 day	72	-	cured	Yes
22006_2	5 day	54	- Mycoplasma	Improved	Yes

1 These two patients were not evaluable by the reviewer as they failed to satisfy the entry criteria for either an abnormal white blood cell count or an abnormal temperature.

[2] These two patients were identified by the applicant as unevaluable but by the reviewer as relapses since they required additional antibiotic treatment for "pneumonia" following evaluation as "improvement" or "cure" upon completion of the study drug.

Table CAPSS 150-32: Relapse rates (among patients successfully treated at visit 4) per number of evaluable patients at the post-study visit

	Clinical success at visit 4	Clinical relapse at post study
5-day arm	146	7[1] (5%)
10-day arm	141	2 (1%)

[1] Includes two patients identified by the applicant as unevaluable but by the reviewer as relapses since they required additional antibiotic treatment after successfully completing the study drug for "pneumonia"

Table CAPSS 150-33: Relapses in the microbiologically evaluable population (Applicant) [From table 21.2]

	Microbiological eradication at visit 4	Clinical relapse at post study	unknown
5-day arm	89	1	5
10-day arm	83	2	4

MO comment: In the subset of patients with microbiological eradication at visit 4, clinical relapses were similar for both arms. However among the larger group of patients with clinical success at visit 4, clinical relapse rates were more frequent in the 5-day arm.

The applicant identified the following superinfections in patients where a new pathogen was found at a follow up visit that was not present on admission.

Table CAPSS 150-34: Superinfections in ITT population

	5-day arm	10-day arm
S pneumoniae	3	1
MRSA	-	3
Candida albicans	-	1
P maltophilia	-	1

MO comment: Of 9 superinfections observed in the applicant's ITT population, those with S pneumoniae were most compatable with relapses in cases where initial cultures may have failed to detect S pneumoniae. Such S pneumoniae superinfections were more frequent in the 5-day arm.

Other endpoints:
The applicant reported resolution or improvement rates for respiratory signs and symptoms at visit 4 (fever, chills, shortness of breath, cough, chest pain, purulent sputum, wheezing, rales, rhonchi, egophony, dullness to percussion and "other").
The results were similar in both treatment arms. (Not reported in this review)

MO conclusions on efficacy:
The applicant has demonstrated equivalent efficacy for the 5-day and 10-day regimens among clinically evaluable patients with community acquired pneumonia. This assessment is based on an assessment of cure 17-21 days after initiation of therapy.

Clinical efficacy also appears equivalent when analyzed according to the severity of disease.

It appears that relapses may be more frequent in the 5-day arm than the 10-day arm (5% versus 1%). The study was not adequately powered to test this possibility so the result is not statistically robust.

Further, the study was not large enough to determine differences in outcome (failures or relapses) between the arms for the subset of patients with positive blood cultures. Nor were there adequate numbers of patients to determine significant differences in the response rates for infections caused by specific organisms e.g. *S pneumoniae, H influenzae*, etc.

The reviewer recommends approval of this new dosing regimen, however labeling should include response rates by organism to demonstrate the small numbers of cases where a microbiological etiology was determined.
Labeling should also indicate that relapse rates may be higher when the short course regimen is used.

CAPS 171

Objective: To further evaluate clinical efficacy and safety of a 5-day course of levofloxacin (750mg IV or PO q.d.) in the treatment of "mild to severe" CAP and to obtain more experience in the treatment of a broad array of pathogens

Study design: A multi-center, non-comparative study

CAPS 171 was an open label non-comparative study where all patients were treated with levofloxacin 750mg QD for 5 days. In all other respects, the procedures and practices were the same as those applied to patients in the 5-day arm of CAPS 150. The table below highlights the most important similarities and differences between the two studies.

Comparisons of study designs for CAPS 150 and CAPS 171

Study	CAPS 171	CAPS 150
Design	Non comparative	Randomized comparative blinded
population	Outpatients or hospitalized or nursing home residents <14 days	Same
Inclusion criteria	No differences	No differences
Exclusion criteria	Creatinine clearance <20ml/min	Creatinine clearance <50ml/min
	No other differences	No other differences
Study drug	Levaquin capsules 750mg Or Levaquin parenteral solution (750mg/vial)-1 vials	Levaquin capsules 750mg (over encapsulated) Or Levaquin parenteral solution (500mg/vial)-1 ½ vials
Dosage adjustment in renal failure	CrCL 20-49 750mg q48h If falls during therapy - CrCl 10-19 500mg q48h	None (CrCl < 50 excluded)
Study schedule	Visit 3 day 12-16	Visit 3 day12-16
	Visit 4 (post study) day 26-33	Visit 4 (post therapy) day 17-21
	none	Visit 5 (post study) day 31-38
Procedures	No significant differences	No significant differences
Evaluation of clinical efficacy	12-16 days after initiation of therapy	12-16 or 17-21 days after initiation of

		therapy (FDA used 17-21 days)
Determination of clinical and microbiological outcomes	No difference	No difference
Safety	Serious adverse events reported up to 30 days after therapy	Serious adverse events reported up to 14 days after therapy

MO comment: The eligible population for this study differed from CAPS 150 only in the fact that patients with creatinine clearances <50ml/min were included and dose adjustments were made for these patients.

Results:
Study centers: 39 (all USA)
Patients enrolled: 124

Table CAPSS 171-1: populations for analysis (applicant)

	CAPS 171	CAPS 150
Randomized	124	530
ITT	123	528
Safety	123	521
Clinically evaluable	74	390
Microbiologically evaluable	34	195

The demographic characteristics of the patients in this study were compared with those of the patients in CAPS 150 (see below)

Table CAPSS 171-2: Demographics (all randomized patients) listed as %

	CAPS 171 (n=123)	CAPS 150 (n=538)	
		5 day regimen (n=256)	10 day regimen (n=272)
% Female	42	42	40
Race			
% Caucasian	65	70	67
% Black	27	20	24
% Asian	3	2	1
% Hispanic	5	7	8
% Other		1	<1
Mean weight	178 ± 49	176± 43	177± 45
Age			
% <=45	29	37	31
% 46-64	26	32	33
% >=65	46	31	36
Fine score			
% I/II (milder)	53	61	55

	CAPS 171 (n=123)	CAPS 150 (n=538)	
		5 day regimen (n=256)	10 day regimen (n=272)
% III/IV (more severe)	47	40	45
% Non-smoker	39	33	38
% No history of alcoholism	94	84	84

MO comment: Patients in CAPS 171 were older and their Fine scores were generally higher than the patients in CAPS 150. (Notably, age itself contributes significantly to the Fine score)

Of the 123 enrolled, there were 13 early withdrawals (adverse event (7), clinical failure (1), other (5)) and 2 were lost to follow-up. Of the 108 completing therapy, 82 completed the post-study visit.

Table CAPSS 171-3: Treatment compliance

Therapy 4-5 days	99 (80.5%)
Therapy 6-10 days	12 (9.8%)

MO comment: A significant proportion exceeded the proposed duration of therapy. These patients may represent treatment failures where the physician judged the duration of therapy to be inadequate

Protocol deviations potentially affecting the evaluation of efficacy (concomitant antimicrobials, violations in duration of therapy, other)

1) Waivers were granted to 13 patients who entered the study despite failing to meet entry criteria as describe below:

Table CAPSS 171-4: Waivers for inclusion in study

Reason for waiver		Evaluablity
No appropriate infiltrate on CXR	2 (3004, 6010)	not clinically evaluable
Normal WBC and temp	1	not clinically evaluable
Absence of fever (on antipyretics)	10	clinically evaluable

2) other protocol deviations

Table CAPSS 171-5: Protocol deviations

Protocol deviation	**Number of patients**	**Applicant's evaluation**
Wrong treatment or incorrect dose (dosing was modified for renal compromise and exceeded 5 days)	15 (included 8 whose dosing was modified for renal compromise and exceeded 5 days) (9022, 10004, 10010, 35002, 38004, 41001, 91002, 91004)	Not included in clinically evaluable group
Received antimicrobials prior to post-therapy (visit 3)	7 (9021, 10006,23003, 75001, 79003, 83002, 99001)	Not included in clinically evaluable group
Received antimicrobials between post therapy visit (visit 3) and post study	5	included in clinically evaluable group
Did not return for test of cure visit (day 7-14)	19 (10 one day early, 9 two to nine days out) Investigators recorded success in 18, unevaluable in 1	Excluded from clinically evaluable group

Protocol deviation	Number of patients	Applicant's evaluation
Lost to follow up	4	Excluded from clinically evaluable group
Other protocol violation	1	Excluded from clinically evaluable group

In all, 49/123 patients (40%) were excluded from the clinically evaluable population

MO comment: The number of patients excluded was very high. The most common single reason was patients not returning during the test of cure window. It is more likely that patients excluded on this basis were successes rather than failures where the impetus to seek follow up might have been stronger. Indeed the investigators reported success in 18 of these patients when they were seen outside of the test-of-cure window. Exclusion of these patients is more likely to lead to an underestimate of efficacy than an overestimate of efficacy.
The second largest group of exclusions (15 patients) was for dosing errors. Most of these (8/15) were the result of dosing modifications made for patients with renal insufficiency. While this weakens the data available on patients with renal failure it is unlikely to influence the success rates in the patients with normal renal function.

The exclusion of 49 patients compromises the strength of the conclusions from this study.

Microbiological efficacy could not be assessed in 89/123 subjects. In 70 of these the reason was that infection was not bacteriologically proven.

Clinically evaluable population:
The clinically evaluable population included 74 patients, with demographic characteristics similar to those of the entire enrolled population (data not shown).
The mean age was 60.3 years (range 27-93). All exhibited an acute inflammatory infiltrate on Chest X Ray. Cough was present in 98.6%, shortness of breath in 85.1% and purulent sputum in 77%.

Efficacy evaluation:
Disease severity was categorized as:
- Milder- Fine class I/II (Fine score ≤70)
- More severe - Fine class III/IV (Fine score >70 and ≤ 130)

Table CAPSS 171-6: Comparison of proportion of patients with Fine score >70 and ≤ 130 (more severe disease)

	CAPS 171	CAPS 150	
		5-day	10-day
ITT population	58/123 (47%)	101/256 (39%)	123/272 (45%)
Clinically evaluable population	32/74 (43%)	76/198 (38%)	86/192 (45%)
Microbiologically evaluable population	19/34 (56%)	36/103 (35%)	33/92 (36%)

Comment: Distribution of Fine scores was similar for CAPS171 and the 10-day arm of CAPS 150 in the ITT and clinically evaluable populations. Among the microbiologically evaluable, patients in CAPS 171 had higher scores (more severe illness).

In view of the large number of patients in the ITT population that were not clinically evaluable the reviewer considered the clinically evaluable population a better reflection of drug efficacy.

Efficacy in the clinically evaluable population:

Table CAPSS 171-7: clinical success rates

	CAPS 171[1]	CAPS 150[2]	
		5 day	10 day
Clinical success	59/74 (79.7%)	146/159 (92%)	141/154 (92%)

[1] test of cure 12-16 days post initiation of therapy
[2] test of cure 17-21 days post initiation of therapy

Table CAPSS 171-8: Clinical efficacy (clinically evaluable population)

	CAPS 171	CAPS 150	
	n=74	5 day n=164	10 day n=154
Visit 3 (12-19 days after enrollment)			
No record	-	2	1
Cure	35 (47.3%)	99 (61%)	82 (54%)
Improved	24 (32.4%)	53 (38%)	60 (39%)
Failure	15 (20.3%)	10 (6%)	11 (7%)
Uneval	-	0	0
Post study			
No record	4	5	4
Unable to eval	2	8	3
Cured	49/68 (72%)	119 (79%)	123 (84%)
Improved		12 (8%)	9 (6%)
failure	15/68 (22%)	13 (9%)	13 (9%)
relapse	4/68 (5.8%)	7 (5%)	2 (1%)

MO comment:
The test of cure for CAPS 171 took place at the equivalent time to visit 3 in study CAPS 150
Failure rates were almost 4 times higher in CAPS 171
The applicant attributes this disparity to the fact that patients in CAPS 171

- *were older,*
- *had higher fine scores and*
- *Included patients with more severe renal dysfunction than were included in CAPS150.*

Relapses:

Table CAPSS 171-9: Clinical relapses reported in the ITT population

Patient number	Fine score	Pathogen
6005	70	*M catarrhalis*
6008	71	*E agglomerans*
7002	82	-
9019	32	-
10010	102	*S pneumoniae/S aureus*

MO comment: Among the 5 relapses, Fine scores were by and large >70. There was no significant feature distinguishing these patients from the rest of the study population, in terms of admission pathogen.

Subgroup analysis by severity of disease:
Disease severity was categorized as:

- Milder- Fine class I/II (Fine score ≤70)

- More severe - Fine class III/IV (Fine score >70 and ≤ 130)

Table CAPSS 171-10: Failure rates by fine risk category:

	Milder			More severe		
	CAPS 171[1]	CAPS 150[2]		CAPS 171[1]	CAPS 150[2]	
		5-day	10-day		5-day	10-day
Failure rate	5/42 (11.9%)	8/98 (8%)	4/82 (5%)	10/32 (31.3%)	5/61 (8%)	9/72 (13%)

[1] test of cure 12-16 days post initiation of therapy
[2] test of cure 17-21 days post initiation of therapy

MO comment: The disparately high failure rate in CAPS 171 was largely due to the patients with more severe disease.

Was the failure rate largely accounted for by patients with renal failure?
To address this, the reviewer identified 17 patients among the 74 clinically evaluable patients for whom dosage adjustments were made because of renal dysfunction. Outcomes for those with and without dosage adjustment based on renal dysfunction are shown below.

Table CAPSS 171-11: outcome in patients according to renal function

	Normal renal function	Renal dysfunction
Cured	32/57 (56%)	3/17 (17.6%)
Improved	15/57 (26%)	9/17 (52.9%)
Failed	10/57 (17.5%)	5/17 (29.4%)

One third of the failures in this study occurred among the 17 patients with renal failure (23% of the study population) suggesting that patients with renal failure accounted significantly for the high failure rate in this study. However, the 17.5% failure rate in patients with normal renal function in this study is still higher than the failure rate seen in study CAPS150 of 8% (see page 23) among patients allocated to the 5-day treatment arm.

Blood cultures:

The pathogen and clinical outcome for nine patients with bacteremia at enrollment are described below.

Table CAPSS 171-12: Clinical outcome for patients with bacteremia

Patient number	Pathogen	Outcome
9011		Cured
9017	*S pneumoniae*	Unable to evaluate
9022	*S pneumoniae*	Cured
22001	*S pneumoniae*	Unable to evaluate
3801	*S pneumoniae*	Improved
75002	*S pneumoniae*	Improved
78001	*S pneumoniae*	Failure
99002		Cured
106002	*S pneumoniae*	Failure

MO comment: Seven of the nine positive blood cultures on admission yielded S pneumoniae. Of the 5 evaluable patients with S pneumoniae bacteremia, 2 were clinical failures. These results appear consistent with the poorer prognosis expected among patients with S pneumoniae bacteremia.

Deaths:
Six patients participating in the study died. The causes of death are listed below:

Table CAPSS 171-13: Listing of deaths in study patients

Patient number	Cause of death	Day of death
04002	"pulmonary carcinoma"	
9016	Cardiac arrest/respiratory depression	
17001	Abscess/circulatory failure/pancreatitis/pericarditis/acute renal failure	
35003	"pulmonary carcinoma" heart block	
38001	Arrhythmia/cardiac failure/ cerebrovascular disorder	
91002	"pulmonary carcinoma"	

MO comment: The six deaths did not appear to have resulted from a failure of therapy or from a drug-related adverse event. All but one of the deaths occurred at least 5 days after completion of therapy. One death occurred on day 2. Three of the deaths were from "pulmonary carcinoma" indicating the high prevalence of serious concomitant illnesses in this study population.

Resolution at test-of-cure among patients with these symptoms at baseline:
Fever 92.2%
Chills 89.4%
Purulent sputum 78.9%
Chest pain 71.1%
Shortness of breath 44.4%
Cough 41.1%

MO comment: The symptoms of shortness of breath and cough which persisted in many patients may either indicate failure of treatment of pneumonia or persistence of underlying chest disease.

Radiological responses at test-of-cure
Of the 74 clinically evaluable patients with baseline X-rays, radiological assessment at test of cure was as follows:
X-ray not done 39.2%
Resolved 18.9
Improved 25.7%
No change 6.8%
Worsened 9.5%

MO comment: While complete resolution would not be anticipated at this early follow-up visit, the worsening reported in 9.5% was frequent. This too may either indicate failure of treatment of pneumonia or persistence of underlying chest disease

Microbiological responses at test-of cure

Table CAPSS 171-14: Eradication rates by pathogen (FDA)

	CAPS 171	CAPS 150			
		5-day arm		10-day arm	
Typical pathogens	Eradication rate	Eradication rate	unknown	Eradication rate	unknown
S pneumoniae	6/6	19/20	4	16/20	5
H influenzae	5/6	9/9	0	10/12	2
H parainfluenzae	7/7	9/9	0	8/9	1
Atypical pathogens*					

M pneumoniae	11/12	27/29	2	24/26	2
C pneumoniae	4/5	15/17	0	10/10	1

* Rates for atypical pathogens in this table were calculated using the applicant's diagnostic criteria.

Clinical outcomes for patients with identified pathogens are shown below.

Table CAPSS 171-15: Clinical success rates for the Pathogens of Primary Interest

	CAPS 171	CAPS 150	
		5-day arm	10-day arm
Typical pathogens			
S pneumoniae	5/6	18/20	17/20
H influenzae	5/6	12/12	11/12
H parainfluenzae	6/7	10/10	8/9
Atypical pathogens*			
M pneumoniae	11/12	26/27	24/26
C pneumoniae	4/5	13/15	6/6

MO comment: Very small numbers of evaluable patients were identified with microbiological pathogens. For these few patients, numerical rates for clinical success or microbiological eradication were high. Clinical success rates were slightly lower than bacterial eradication rates for some of the pathogens.

Of 47 pathogens identified and tested for drug susceptibility, three isolates were resistant to levofloxacin.

Microbiological Eradication rates by patient:
The applicant reported eradication of all pathogens in 27/34 microbiologically evaluable patients, persistence in 6 and an unknown response in one.

Super-infections and new infections:

Table CAPSS 171-16: Superinfections and new infections

Superinfection (absent at admission and identified prior to the post-therapy visit)	New infection (absent at admission and identified after the post-therapy visit)
MRSA (1)	
Mycobacterium (1)	
	B catarrhalis (1)

MO conclusions on efficacy:

The overall failure rate in this study was substantially higher than the failure rate seen in study CAPS 150. This is accounted for by differences in the populations enrolled in the two studies. In this study, patients were somewhat older, fine scores were higher, a significant number of patients with renal dysfunction requiring dosage alteration where included, and among the patients who died it was apparent that there was a high prevalence of significant co-morbid conditions.

Failure rates were notably high in patients with renal dysfunction although the criteria for failure were subjectively determined by the investigators, and other conditions such as pulmonary edema or pulmonary embolus may have confounded the assessment.

A large percentage of enrollees could not be evaluated, limiting the statistical strength of the study.

Pathogens were identified in a minority of patients (34) and provided limited additional evidence of efficacy to the etiologically confirmed infections in CAPS 150.

Given the older age and higher morbidity in this population, the poorer outcome appears consistent. The efficacy rates seen in study CAPS150 may be a truer representation of antibacterial efficacy of levofloxacin in patients with CAP, than the efficacy rates seen in study CAPS 171 where comorbidity may have confounded the assessment of efficacy.

Appendix 2

CAPSS-150: Incidence of Adverse Events, by Body System. Table reproduced from applicant report.

Table 31: Incidence of Adverse Events Summarized by Body System: Safety Evaluable Population (Study CAPSS-150)

Body System	Levofloxacin 750 mg qd 5-day Regimen[2] (N=256)		Levofloxacin 750 mg qd 5-day Regimen (Through 19 Days Post Last Dose)[2] (N=256)		Comparator[3] (N=265)		95% Confidence Interval[4]
	n	(%)	n	(%)	n	(%)	
Gastrointestinal System Disorders	52	(20.3)	53	(20.7)	58	(21.9)	(-5.6, 8.8)
Body as A Whole-General Disorders	42	(16.4)	44	(17.2)	58	(21.9)	(-1.5, 12.4)
Respiratory System Disorders	39	(15.2)	40	(15.6)	46	(17.4)	(-4.4, 8.7)
Central & Peripheral Nervous System Disorders	31	(12.1)	33	(12.9)	23	(8.7)	(-8.9, 2.0)
Psychiatric Disorders	31	(12.1)	31	(12.1)	42	(15.8)	(-2.4, 9.9)
Skin and Appendages Disorders	18	(7.0)	20	(7.8)	19	(7.2)	(-4.5, 4.7)
Metabolic and Nutritional Disorders	16	(6.3)	17	(6.6)	24	(9.1)	(-1.9, 7.6)
Resistance Mechanism Disorders	13	(5.1)	13	(5.1)	10	(3.8)	(-5.0, 2.4)
Cardiovascular Disorders, General	10	(3.9)	11	(4.3)	11	(4.2)	(-3.3, 3.8)
Urinary System Disorders	9	(3.5)	9	(3.5)	5	(1.9)	(-4.6, 1.4)
Heart Rate and Rhythm Disorders	8	(3.1)	9	(3.5)	11	(4.2)	(-2.4, 4.4)
Platelet, Bleeding & Clotting Disorders	7	(2.7)	7	(2.7)	4	(1.5)	(-3.9, 1.4)
Red Blood Cell Disorders	6	(2.3)	6	(2.3)	3	(1.1)	(-3.7, 1.2)
Musculoskeletal System Disorders	5	(2.0)	5	(2.0)	7	(2.6)	(-2.1, 3.5)
Liver and Biliary System Disorders	5	(2.0)	5	(2.0)	8	(3.0)	(-1.8, 3.9)
Myo-Endo-Pericardial & Valve Disorders	3	(1.2)	4	(1.6)	2	(0.8)	(-2.3, 1.5)
Vascular (Extracardiac) Disorders	3	(1.2)	3	(1.2)	2	(0.8)	(-2.3, 1.5)
Application Site Disorders	3	(1.2)	3	(1.2)	3	(1.1)	(-2.1, 2.0)
Vision Disorders	2	(0.8)	2	(0.8)	5	(1.9)	(-1.1, 3.3)
Reproductive Disorders, Female[5]	2	(1.9)	2	(1.9)	3	(2.8)	(-3.5, 5.5)
Neoplasm	2	(0.8)	3	(1.2)	3	(1.1)	(-1.5, 2.2)
Secondary Terms	2	(0.8)	2	(0.8)	7	(2.6)	(-0.5, 4.3)
Hearing and Vestibular Disorders	1	(0.4)	1	(0.4)	2	(0.8)	(-1.1, 1.9)
Special Senses Other, Disorders	1	(0.4)	1	(0.4)	1	(0.4)	(-1.3, 1.2)
Reproductive Disorders, Male[6]	1	(0.7)	2	(1.4)	1	(0.6)	(-2.2, 2.1)
Foetal Disorders	1	(0.4)	1	(0.4)	0	(0.0)	(-1.4, 0.6)
Endocrine Disorders	0	(0.0)	0	(0.0)	4	(1.5)	(-0.2, 3.2)
White Cell and Res Disorders	0	(0.0)	0	(0.0)	5	(1.9)	(0.1, 3.7)
Total Subjects With Adverse Events	148	(57.8)	150	(58.6)	158	(59.6)	(-6.8, 10.5)

[1] Table includes adverse events which began on-therapy or up to 14 days after the last active dose of study drug unless otherwise specified (as in second column).
[2] Two-sided 95% confidence interval (with continuity correction) around the difference between treatments (comparator minus levofloxacin 750 mg q.d. 5-day regimen) in incidence of adverse events that began on-therapy or up to 14 days after the last active dose of study drug.
[3] Percentages calculated from the total number of women evaluable for safety in each treatment group. The total number of women who received the levofloxacin 750 mg q.d. 5-day regimen was 108 and the total number of women who received comparator was 107.
[4] Percentages calculated from the total number of men evaluable for safety in each treatment group. The total number of men who received the levofloxacin 750 mg q.d. 5-day regimen was 148 and the total number of men who received comparator was 158.
NOTE: Comparator: levofloxacin 500 mg q.d. 10-day regimen.

Appendix 3
CAPSS-171: Incidence of Adverse Events, by Body System. Table reproduced from applicant report.

Table 32: Incidence of Adverse Events Summarized by Body System: Safety Evaluable Population (Study CAPSS-171)

	Levofloxacin 750 mg q.d. 5-day Regimen (N=123)	
Body System	n	(%)
Gastrointestinal System Disorders	32	(26.0)
Psychiatric Disorders	31	(25.2)
Body as a Whole-General Disorders	28	(22.8)
Respiratory System Disorders	24	(19.5)
Metabolic and Nutritional Disorders	17	(13.8)
Central & Peripheral Nervous System Disorders	12	(9.8)
Heart Rate and Rhythm Disorders	8	(6.5)
Resistance Mechanism Disorders	8	(6.5)
Musculoskeletal System Disorders	6	(4.9)
Cardiovascular Disorders, General	6	(4.9)
Platelet, Bleeding & Clotting Disorders	5	(4.1)
Application Site Disorders	5	(4.1)
Liver and Biliary System Disorders	4	(3.3)
Urinary System Disorders	4	(3.3)
Skin and Appendages Disorders	3	(2.4)
Red Blood Cell Disorders	3	(2.4)
Neoplasm	3	(2.4)
Secondary Terms	3	(2.4)
Vascular (Extracardiac) Disorders	2	(1.6)
White Cell and RES Disorders	1	(0.8)
Reproductive Disorders, Male[a]	1	(1.4)
Reproductive Disorders, Female[b]	1	(1.9)
Total Subjects With Adverse Events	73	(59.3)

[a] Percentages calculated from the total number of men evaluable for safety. The total number of men who received the levofloxacin 750 mg q.d. 5-day regimen was 71.
[b] Percentages calculated from the total number of women evaluable for safety. The total number of women who received the levofloxacin 750 mg q.d. 5-day regimen was 52.
NOTE: Table includes adverse events which began on-therapy or up to 14 days after the last active dose of study drug.

Appendix 4

CAPSS-150: Summary of Subjects who Died. Table reproduced from applicant report.

Table 33: Summary of Subjects Who Died
(Study CAPSS-150)

Treatment Group Subject Number	Age (yrs)	Gender (M/F)	Days to Study at Death	Adverse Event(s) Leading to Death	Relationship to Study Drug	Study Day[1]
Levofloxacin 750 mg qd 5-day Regimen						
6027	62	M		Myocardial Infarction	Not Related	
38018	70	M		Respiratory Failure	Not Related	
71001	73	M		Myocardial Infarction	Not Related	
79008	76	F		End Stage COPD	Not Related	
				Sepsis	Not Related	
91015	73	M		Bronchiectasis	Not Related	
				Community Acquired Pneumonia Condition Aggravated	Not Related	
				Respiratory Failure	Not Related	
Comparator						
3003	51	M		Acute Pulmonary Edema (Worsening CHF)	Not Related	
				Cardiac Arrest	Not Related	
				Respiratory Arrest	Not Related	
				Syncope	Not Related	
				Unstable Angina	Not Related	
12001	58	M		Worsening of Pneumonia	Not Related	
15011	78	F		Cardiac Arrest	Not Related	
				Oliguria	Not Related	
				Respiratory Failure	Not Related	
37006	76	F		Right Leg Arterial Thrombosis	Doubtful	
37014	79	M		Acute Myocardial Infarction	Not Related	
				Cardiac Arrest	Not Related	
				Respiratory Arrest	Not Related	
38003	65	M		Atrial Fib	Not Related	
				Atrial Fibrillation	Not Related	
				Respiratory Failure	Not Related	
57002	79	M		Endocarditis	Not Related	
				Mitral Insufficiency	Not Related	
99002	48	M		Multiple Organ Failure	Not Related	
134014	61	M		Respiratory Insufficiency	Not Related	

[1] Study day at event onset. PT refers to the number of days post-therapy relative to the last day of study drug administration (Day 0).
NOTE: Comparator=levofloxacin 500 mg q.d. 10-day regimen.

Appendix 5

CAPSS-171: Summary of Subjects who Died. Table reproduced from applicant report.

Table 36: Summary of Subjects Who Died
(Study CAPSS-171)

Subject Number	Age (yrs)	Gender (M,F)	Days in Study	Adverse Event(s) (Verbatim) Leading to Death	Relationship to Study Drug	Study Day*
4002	50	F		Lung CA With Mets	Doubtful	
9016	38	M		Cardiac Arrest	Not Related	
				Pulmonary Arrest	Not Related	
17001	31	M		Abscess[b]	Not Related	
				Acute Renal Failure	Not Related	
				Condition Aggravated	Not Related	
				Pancreatitis	Not Related	
				Pericarditis	Not Related	
				Respiratory Failure	Not Related	
				Shock	Not Related	
35003	83	M		Heart Block	Not Related	
				Hilar Mass Class V - Non Small Cell Lung Cancer	Not Related	
38001	77	F		Arrythmia	Not Related	
				Cerebral Vascular Accident	Not Related	
				Congestive Heart Failure	Not Related	
				Hypotension	Not Related	
91002	77	M		Worsening of NSCLC	Not Related	

* Study day at event onset. PT refers to the number of days posttherapy relative to the last day of study drug administration (Day 0).
[b] Lung abscess.

Appendix 6

CAPSS-150: Incidence of Adverse Events Resulting in Discontinuation. Table reproduced from applicant report.

Table 35: Incidence of Adverse Events Resulting in Discontinuation of Study Drug Summarized by Body System and Primary Term: Safety Evaluable Population (Study CAPSS-150)

	Levofloxacin 750 mg qd 5-day Regimen (N=256)		Comparator (N=265)	
Body System/Primary Term	n	(%)	n	(%)
All Body Systems	18	(7.0)	22	(8.3)
Body as A Whole-General Disorders				
Allergic Reaction	1	(0.4)	0	(0.0)
Asthenia	0	(0.0)	1	(0.4)
Condition Aggravated	3	(1.2)	5	(1.9)
Drug Level Increased	1	(0.4)	0	(0.0)
Fever	2	(0.8)	1	(0.4)
Multiple Organ Failure	0	(0.0)	1	(0.4)
Oedema	0	(0.0)	1	(0.4)
Oedema Peripheral	1	(0.4)	0	(0.0)
Rigors	1	(0.4)	0	(0.0)
Central & Peripheral Nervous System Disorders				
Dizziness	0	(0.0)	1	(0.4)
Dystonia	1	(0.4)	0	(0.0)
Headache	1	(0.4)	1	(0.4)
Hypertonia	1	(0.4)	0	(0.0)
Tremor	1	(0.4)	0	(0.0)
Endocrine Disorders				
Sialoadenitis	0	(0.0)	1	(0.4)
Foetal Disorders				
Aortic Stenosis	1	(0.4)	0	(0.0)
Gastrointestinal System Disorders				
Abdominal Pain	0	(0.0)	1	(0.4)
Diarrhoea	0	(0.0)	1	(0.4)
Nausea	3	(1.2)	1	(0.4)
Vomiting	3	(1.2)	0	(0.0)
Heart Rate and Rhythm Disorders				
Cardiac Arrest	0	(0.0)	2	(0.8)
Fibrillation Ventricular	1	(0.4)	0	(0.0)
Tachycardia	1	(0.4)	0	(0.0)
Liver and Biliary System Disorders				
Cholecystitis	0	(0.0)	1	(0.4)
Cholelithiasis	0	(0.0)	1	(0.4)
Hepatic Necrosis	1	(0.4)	0	(0.0)
Hepatitis	1	(0.4)	0	(0.0)
Metabolic and Nutritional Disorders				
Oedema Periorbital	0	(0.0)	1	(0.4)
Musculoskeletal System Disorders				
Tendon Disorder	1	(0.4)	0	(0.0)
Myo Endo Pericardial & Valve Disorders				
Endocarditis	1	(0.4)	1	(0.4)
Mitral Insufficiency	0	(0.0)	1	(0.4)
Neoplasm				
Adenocarcinoma NOS	1	(0.4)	0	(0.0)
Psychiatric Disorders				
Agitation	0	(0.0)	1	(0.4)
Confusion	0	(0.0)	1	(0.4)
Drug Abuse	1	(0.4)	0	(0.0)
Hallucination	1	(0.4)	1	(0.4)

NOTE: Comparator=levofloxacin 500 mg q.d. 10-day regimen.
Table includes adverse events which began on-therapy or up to 14 days after the last active dose of study drug.

Appendix 7

CAPSS-171: Discontinuation fro Therapy due to Adverse Events. Table reproduced from applicant report.

Table 40: Subjects Who Discontinued Therapy Due to Adverse Events: Safety Evaluable Population (Study CAPSS-171)

Treatment Group Subject Number	Age (yrs)	Adverse Event (Primary Term)	Study Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
Levofloxacin 750 mg q.d. 5-day Regimen						
3002	28	Allergic Reaction[c,d]	2 (0 PT)	Moderate	Very Likely	2
		Cholelithiasis[c]	1 (-1 PT)	Moderate	Not Related	
4001	70	Condition Aggravated[c,d]	4 (0 PT)	Moderate	Doubtful	4
		Herpes Simplex[c]	4 (0 PT)	Mild	Doubtful	
9003	64	Hepatic Function Abnormal[c]	3 (0 PT)	Moderate	Possible	3
9016	38	Cardiac Arrest[c,d]	2 (1 PT)	Marked	Not Related	1
		Respiratory Depression[c,d]	2 (1 PT)	Marked	Not Related	
22003	38	Allergic Reaction[c,d]	1 (0 PT)	Moderate	Very Likely	1
		Insomnia	1 (0 PT)	Moderate	Not Related	
57001	58	Diarrhoea[d]	2 (-1 PT)	Mild	Possible	3
		Paroniria[d]	2 (-1 PT)	Mild	Possible	
89001	60	Pain[d]	1 (-1 PT)	Marked	Possible	2

[a] Relative to start of therapy. NOTE: PT Refers to the number of days of posttherapy relative to the last day of study drug administration (Day 0).
[b] Based on investigator assessment.
[c] Serious adverse event.
[d] Subject discontinued therapy due to this adverse event.

Appendix 8

CAPSS-150: Incidence of Treatment-emergent Markedly Abnormal Laboratory Values. Table reproduced from applicant report.

Table 37: Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Safety Evaluable Population (Study CAPSS-150)

	Levofloxacin 750 mg qd 5-day Regimen		Comparator	
Laboratory Test (Units)	Proportion[a]	%	Proportion[a]	%
Hematology				
Decreased Hemoglobin (g/dL)	5/254	2.0	5/260	1.9
Decreased Neutrophils (%)	1/254	0.4	2/260	0.8
Decreased Lymphocytes (%)	3/254	1.2	8/260	3.1
Decreased Platelet Count ($x10^3/\mu L$)	1/249	0.4	0/256	0.0
Blood Chemistry				
Decreased Glucose (mg/dL)	3/252	1.2	8/261	3.1
Elevated Glucose (mg/dL)	9/252	3.6	5/261	1.9
Elevated BUN (mg/dL)	3/253	1.2	4/262	1.5
Elevated LDH (U/L)	1/249	0.4	0/260	0.0
Elevated Creatinine (mg/dL)	2/253	0.8	2/262	0.8
Elevated Alkaline Phosphatase (U/L)	1/251	0.4	0/262	0.0
Elevated SGOT (U/L)	4/251	1.6	4/261	1.5
Elevated SGPT (U/L)	9/251	3.6	7/261	2.7
Elevated Bilirubin (mg/dL)	1/253	0.4	1/262	0.4

[a] Numerator=number of subjects with a markedly abnormal laboratory value at posttherapy Visits 3 and/or 4.
Denominator=number of subjects having admission or posttherapy visit data for that analyte. Denominator includes subjects with missing admission values since, in these cases, the absolute value portion of the criterion was applied.

Note: Comparator=levofloxacin 500 mg qd 10-day regimen.

Appendix 9

CAPSS-150: Subjects with Treatment-emergent Markedly Abnormal Laboratory Values. Table reproduced from applicant report.

Table 38: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Safety Evaluable Population (Study CAPSS-150)

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Criterion)	Admission	Posttherapy Visit 3	Posttherapy Visit 4
Levofloxacin 750 mg qd 5-day Regimen						
6013	79	F	Glucose (>200 mg/dL & ≥75% Increase)	75.00	201.00 A	144.00
6024	42	F	Glucose (>200 mg/dL & ≥75% Increase)	101.00	119.00	215.00 A
6026	68	F	Glucose (>200 mg/dL & ≥75% Increase)	126.00	203.00	254.00 A
9009	66	M	Lymphocytes (<1.0 x 10^3/µL & ≥33% Decrease)	-	0.72 A	1.15
12002	58	M	SGOT (>75 U/L & ≥100% Increase)	19.00	122.00 A	39.00
			SGPT (>75 U/L & ≥100% Increase)	13.00	121.00 A	50.00
			Hemoglobin (<12.0 g/dL & >3 g/dL Decrease)	14.20	12.20	10.20 A
15009	76	F	Blood Urea Nitrogen (>40 mg/dL & ≥66% Increase)	14.00	42.00 A	25.00
23005	31	M	Glucose (<70 mg/dL & >33% Decrease)	108.00	123.00	22.00 A
38018	70	M	Creatinine (Rate Blanked) (>1.5 mg/dL & ≥66% Increase)	0.60	0.60	3.50 A
			Blood Urea Nitrogen (>40 mg/dL & ≥66% Increase)	10.00	10.00	88.00 A
38023	52	F	Creatinine (Rate Blanked) (>1.5 mg/dL & ≥66% Increase)	0.80	1.90 A	-
			Total Bilirubin (>1.5 mg/dL & ≥100% Increase)	0.90	4.40 A	-
			SGOT (>75 U/L & ≥100% Increase)	13.00	7919.00 A	-
			Lactic Dehydrogenase (>600 U/L & ≥100% Increase)	211.00	7659.00 A	-
			SGPT (>75 U/L & ≥100% Increase)	8.00	2415.00 A	-
			Glucose (<70 mg/dL & >33% Decrease)	121.00	50.00 A	-
47020	26	M	Hemoglobin (<12.0 g/dL & >3 g/dL Decrease)	-	11.40 A	-
47022	37	F	Hemoglobin (<12.0 g/dL & >3 g/dL Decrease)	-	11.20 A	10.90 A
47028	44	M	SGOT (>75 U/L & ≥100% Increase)	-	72.00	96.00 A
			SGPT (>75 U/L & ≥100% Increase)	-	85.00 A	101.00 A
			Glucose (>200 mg/dL & ≥75% Increase)	-	348.00 A	337.00 A
61005	59	M	Neutrophils (<1.0 x 10^3/µL & ≥33% Decrease)	0.57 A	0.54	0.22 A
63003	73	F	Glucose (<70 mg/dL & >33% Decrease)	110.00	69.00 A	107.00
71007	65	M	SGPT (>75 U/L & ≥100% Increase)	17.00	90.00 A	66.00
78007	45	M	Lymphocytes (<1.0 x 10^3/µL & ≥33% Decrease)	1.41	0.73 A	-
78029	66	M	Hemoglobin (<12.0 g/dL & >3 g/dL Decrease)	-	12.90	11.80 A
78030	48	M	SGPT (>75 U/L & ≥100% Increase)	24.00	116.00 A	112.00 A
78037	56	F	Glucose (>200 mg/dL & ≥75% Increase)	55.00 A	133.00	527.00 A

NOTE: Comparator = levofloxacin 500 mg q.d. 10-day regimen.
Table includes subjects who had markedly abnormal laboratory value(s) at any time point after admission.
Subjects with missing admission values had the absolute value portion of the criterion applied.
A = markedly abnormal value, R = repeat value.

Appendix 10

CAPSS-171: Incidence of Treatment-emergent Markedly Abnormal Laboratory Values. Table reproduced from applicant report.

Table 41: Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Safety Evaluable Population (Study CAPSS-171)

	Levofloxacin 750 mg q.d. 5-day Regimen	
Laboratory Test (units)	Proportion[a]	%
Hematology		
Decreased Hemoglobin (g/dL)	6/117	5.1
Decreased Neutrophils (%)	1/117	0.9
Decreased Lymphocytes (%)	4/117	3.4
Blood Chemistry		
Decreased Glucose (mg/dL)	2/120	1.7
Elevated Glucose (mg/dL)	2/120	1.7
Elevated BUN (mg/dL)	3/120	2.5
Elevated Creatinine (mg/dL)	2/120	1.7
Elevated SGPT (U/L)	3/120	2.5

[a] Numerator=Number of subjects with a markedly abnormal laboratory value at posttherapy (Visit 3). Denominator=Number of subjects having admission or posttherapy visit data for that analyte. Denominator includes subjects with missing admission values since, in these cases, the absolute value portion of the criterion was applied.

Appendix 11

CAPSS-171: Subjects with Treatment-emergent Markedly Abnormal Laboratory Values. Table reproduced from applicant report.

Table 42: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values[a]: Safety Evaluable Population (Study CAPSS-171)

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Criterion)	Admission	Posttherapy (Visit 3)
6009	81	F	Hemoglobin (<12.0 g/dL & >3 g/dL decrease)	-	11.90 A
7001	69	M	Hemoglobin (<12.0 g/dL & >3 g/dL decrease)	13.50	9.90 A
			Lymphocytes (<1.0 x 10^3/µL & ≥33% decrease)	1.39	0.84 A
9002	41	F	Glucose (<70 mg/dL & >33% decrease)	99.00	56.00 A
9003	64	F	SGPT (>75 U/L & ≥100% increase)	-	99.00 A
9005	27	F	Glucose (<70 mg/dL & >33% decrease)	216.00	68.00 A
9010	87	M	Lymphocytes (<1.0 x 10^3/µL & ≥33% decrease)	-	0.44 A
9015	55	F	Blood Urea Nitrogen (>40 mg/dL & ≥66% increase)	26.00	53.00 A
15001	75	M	Creatinine (rate blanked) (>1.5 mg/dL & ≥66% increase)	-	3.50 A
			Blood Urea Nitrogen (>40 mg/dL & ≥66% increase)	-	76.00 A
			Hemoglobin (<12.0 g/dL & >3 g/dL decrease)	-	10.90 A
			Lymphocytes (<1.0 x 10^3/µL & ≥33% decrease)	-	0.97 A
35001	93	M	Blood Urea Nitrogen (>40 mg/dL & ≥66% increase)	27.00	64.00 A
38005	46	M	Glucose (>200 mg/dL & ≥75% increase)	123.00	270.00 A
41001	69	M	Creatinine (rate blanked) (>1.5 mg/dL & ≥66% increase)	-	2.00 A
			Hemoglobin (<12.0 g/dL & >3 g/dL decrease)	-	10.40 A
78001	49	M	SGPT (>75 U/L & ≥100% increase)	11.00	133.00 A
79001	62	M	Neutrophils (<1.0 x 10^3/µL & ≥33% decrease)	1.64	0.35 A
79004	70	F	Hemoglobin (<12.0 g/dL & >3 g/dL decrease)	-	10.20 A
79004	70	F	Lymphocytes (<1.0 x 10^3/µL & ≥33% decrease)	1.11	0.18 A
90001	27	F	SGPT (>75 U/L & ≥100% increase)	32.00	116.00 A
91003	57	M	Glucose (>200 mg/dL & ≥75% increase)	178.00	418.00 A
100001	28	F	Hemoglobin (<12.0 g/dL & >3 g/dL decrease)	-	11.90 A

[a] Table displays subjects who had markedly abnormal laboratory value(s) at posttherapy (Visit 3).
NOTE: Subjects with missing admission values had the absolute value portion of the criterion applied.
KEY: A=markedly abnormal value; R=repeat value.

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/s/

Rigoberto Roca
10/23/03 09:48:59 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

CHEMISTRY REVIEW(S)

NDA CHEMIST'S REVIEW	1. ORGANIZATION: HFD-590	2. NDA NUMBER: 20-634

3. NAME AND ADDRESS OF APPLICANT: *(City and State)*	4. SUBMISSION TYPE:	
The R.W. Johnson Pharmaceutical Research Institute 920 Route 202 P.O. Box 300 Raritan, NJ 08869-0602	Prior Approval	
	5. SUPPLEMENT(S):	
	NUMBER(S):	DATE(S):
	SE2-028	20-DEC-2002

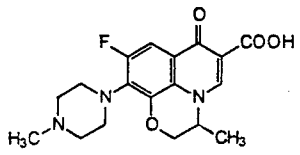
6. NAME OF DRUG:	7. NONPROPRIETARY NAME:
LEVAQUIN® Tablets	levofloxacin tablets

8. SUPPLEMENT(S) PROVIDES FOR: The use of LEVAQUIN® Tablets in the treatment of community-acquired pneumonia utilizing a once daily 750-mg dose of levofloxacin for a duration of 5 days.	9. AMENDMENTS/REPORTS:

10. PHARMACOLOGICAL CATEGORY:	11. HOW DISPENSED:	12. RELATED IND/NDA/DMF(S):
Antibacterial	[X] Rx [ ]OTC	IND 36,627 and 38638; NDA 20-635

13. DOSAGE FORM(S): Tablets	14. POTENCY(IES): 250-, 500- and 750-mg

15. CHEMICAL NAME AND STRUCTURE: *S*-(-)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid



16. MEMORANDA:

EA consult to the Environmental Officer (N. Sager), 06-JAN-2003

17. COMMENTS: This supplemental NDA provides for the use of a 750-mg dose of levofloxacin once daily for five days for treatment of chronic bacterial prostatitis. J&J has provided an updated environmental assessment, which was submitted to the Environmental Officer for consultation. The Environmental Officer issued an updated FONSI on 15-JAN-2003.

18. CONCLUSIONS AND RECOMMENDATIONS: This supplemental application may be approved from a CMC perspective.

19. REVIEWER:	SIGNATURE:	DATE COMPLETED:
Gene W. Holbert, Ph.D.	*{See appended electronic signature page.}*	06-FEB-2003
20. CONCURRENCE: Norman R. Schmuff, Ph.D.	*{See appended electronic signature page.}*	

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/s/

Gene Holbert
2/9/03 02:42:00 PM
CHEMIST

Norman Schmuff
2/13/03 12:22:57 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-027
20-635 / S-026

ENVIRONMENTAL ASSESSMENT

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR
LEVAQUIN® (levofloxacin) Injection

NDA 20-635 / S-027
Treatment of community acquired pneumonia

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Special Pathogens and
Immunological Drug Products
(HFD-590)

January 15, 2003

Environmental Assessment Review #1, NDA 20-635 / S-027
Short course treatment of community acquired pneumonia

LEVAQUIN® (levofloxacin) Injection

EXECUTIVE SUMMARY

A FONSI is recommended

The environmental assessment (EA) dated December 13, 2002 supports the supplemental new drug application submitted by Johnson & Johnson Pharmaceutical R & D, LLC for Levaquin® (levofloxacin) Injection. This EA was prepared in accordance with 21 CFR Part 25. This EA is an update to EAs dated 11/27/96, 10/27/98, 11/4/99, 2/7/2002, 4/17/2002 and 7/10/2002. The most recent EA does not contain new or additional information beyond the new indication, short course treatment of community acquired pneumonia. All submissions evaluate the potential environmental impacts from the use and disposal of levofloxacin. The previous reviews of the previous EAs resulted in FONSIs dated 12/5/96, 12/1/98, 1/4/00, 3/21/02, 7/16/02 and 9/16/2002.

Levofloxacin may enter the aquatic and terrestrial environment from patient use and disposal and is expected to degrade rapidly when exposed to light. Although degradation mechanisms were demonstrated for the aquatic and terrestrial environment, the toxicity of levofloxacin to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (MIC)	Clostridium perfringens = 0.20 ppm Nostoc sp. = 0.4 ppm Bacillus subtilis = 0.06 ppm Trichoderma virde > 1000 ppm Aspergillus niger > 1000 ppm
Daphnia	NOEC < 43 ppm EC_{50} = 320 ppm
Bluegill Sunfish	NOEC = 630 ppm EC_{50} = 950 ppm

REVIEW OF EA SUBMITTED IN NDA 20635 / S-027
Short Course Treatment of community acquired pneumonia

I. **DATE:** December 13, 2002

II **APPLICANT:** Johnson & Johnson Pharmaceutical R & D, LLC

III **ADDRESS:** 1000 Route 202 South
PO Box 300
Raritan, New Jersey 08869-0602

IV PROPOSED ACTION:

Supplemental application (20-635/S-027) is requesting approval of levofloxacin for use in short course treatment of community acquired pneumonia. The additional quantity of levofloxacin required for this new indication will not increase the total amount of levofloxacin manufactured in any of the next 5 years. The total amount of drug substance manufactured for all indications is expected to be NMT ——— Reference: Current EA dated December 13, 2002 and, for comparison, Confidential Appendix I in EA dated April 17, 2002).

Appropriate CMC information was provided in the Original NDA 20-634 dated 12/21/95 (Volume 1.014, page 0303077) and revised data submitted on 10/31/96, 11/27/96, 11/5/99, 3/31/00, 4/17/02 and 7/10/02. All submissions pertain to potential environmental impacts from the use and disposal of levofloxacin. The previous reviews of previous EAs resulted in FONSIs dated 12/5/96, 12/1/98, 1/4/00, 3/21/02, 7/16/02 and 9/16/02.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

Information is provided by cross-reference to NDA 20-634 (Volume 1.014, page 0303077) submitted Dec 21, 1995 and revised data submitted Oct 31, 1996, Nov 27, 1996, Nov 5, 1999, and March 31, 2000.

ADEQUATE

VI ENVIRONMENTAL ISSUES

Information about environmental fate and effects is provided by cross-reference to the EA dated October 26, 1998 submitted in the "urinary tract infection" supplement to NDA 20-634.

Briefly, the lowest minimum inhibitory concentration (MIC) found was [redacted] the soil bacteria, *Bacillus subtilis*. The NOEC for daphnia magna was [redacted] ıe NOEC for blue gill sunfish was [redacted]

The EIC, namely [redacted] lower than values observed above.

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARER

Name, job title and qualifications provided.

ADEQUATE

X CERTIFICATION

Provided.

ADEQUATE

XI APPENDICES

Production estimate provided in Confidential Appendix I

ADEQUATE

SUMMARY

Levofloxacin is a chemically synthesized drug currently approved for treatment of:

(a) community acquired pneumonia
(b) acute exacerbation of chronic bronchitis
(c) acute maxillary sinusitis
(d) complicated and uncomplicated urinary tract infections
(e) acute pylonephritis
(f) complicated and uncomplicated skin and skin structure infections
(g) nosocomial pneumonia

The supplements pertaining to treatment of (a) inhalation anthrax, post exposure and (b) chronic bacterial prostatitis are not yet approved.

Supplemental application (20-635/S-027) is requesting approval of levofloxacin for use in short course treatment of community acquired pneumonia. The additional quantity of levofloxacin required for this new indication will not increase the total amount of levofloxacin manufactured in any of the next 5 years. (Reference: Current EA dated December 13, 2002 and, for comparison, Confidential Appendix I in EA dated April 17, 2002).

The EIC (aquatic) for levofloxacin based on NMT [redacted] per year remains unchanged a[redacted] he FONSIs approved January 4, 2000, March 21, 2002, July 16, 2002 and Sept 16, 2002 were based on the exact same production estimate.)

New ecotoxicity data are not provided in an EA dated December 13, 2002.

The conclusion from the previous submissions that a FONSI is appropriate is still valid.

Review by: Florian Zielinski on January 15, 2003
Chemist, Center for Drug Evaluation and Research

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/s/

Florian Zielinski
1/16/03 10:32:13 AM
ENV ASSESSMENT

Nancy Sager
1/28/03 03:37:46 PM
ENV ASSESSMENT

Yuan-Yuan Chiu
2/3/03 10:01:42 AM
CHEMIST
Concurred

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LEVAQUIN® (levofloxacin) Injection

NDA 20-635 S-027
Treatment of Community Acquired Pneumonia

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Special Pathogens and
Immunological Drug Products
(HFD-590)

January 15, 2003

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-635 S-027
Short Course Treatment of community acquired pneumonia

LEVAQUIN ® (levofloxacin) Injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

This supplement requests approval of Levaquin® (levofloxacin) Injection for use in the short course treatment of community acquired pneumonia. In support of its supplemental new drug application for levofloxacin, Johnson & Johnson R & D, LLC prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Levofloxacin is a chemically synthesized drug currently approved for use in the treatment of several types of infections.

Levofloxacin may enter the aquatic and terrestrial environment from patient use and disposal and is expected to degrade rapidly when exposed to light. Although degradation mechanisms were demonstrated for the aquatic and terrestrial environment, the toxicity of levofloxacin to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

I. **DATE:** December 13, 2002

II. **NAME OF APPLICANT:** Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

III. **ADDRESS:** 920 U.S. Route 202 South, P.O. Box 300 Raritan, NJ 08869

IV. **PROPOSED ACTION**

Supplemental New Drug Applications (sNDA) for LEVAQUIN® (levofloxacin) Tablets and LEVAQUIN® (levofloxacin) Injection are being submitted for the indication of short course treatment of community acquired pneumonia utilizing 750mg dosage. An environmental assessment (EA) is required by 21 CFR Part 25.20 (l).

Levofloxacin Tablets are the subject of NDA 20-634, approved December 20, 1996. In addition, an injectable formulation of levofloxacin is the subject of NDA 20-635, approved December 20, 1996, and a supplement to that NDA for treatment of chronic bacterial prostatitis, is being submitted concurrently. Both the tablet and injection are approved for treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinusitis, complicated urinary tract infection, acute pylonephritis, uncomplicated and complicated skin and skin structure infection, uncomplicated urinary tract infection. This sNDA is for the short course treatment of community acquired pneumonia utilizing 750mg dosage.

The maximum expected environmental concentration (MEEC) given in Section VI of this sNDA (as well as the sNDA for the injectable formulation) is based on the total projected 5th year demand for the drug substance. Since both the drug substance and drug product formulation remain unchanged, and since environmental fate and effects information for levofloxacin has previously been submitted, a cross-reference to NDA 20-634 is provided in lieu of much of the information typically found in Sections V and VI of the environmental assessment.

Levofloxacin Tablets and Levofloxacin Injection will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages according to their internal handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

V. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

Cross-refer to Levofloxacin Tablets NDA 20-634 (Volume 1.014, page 0303077), submitted December 21, 1995 and to the revised data submitted on October 31, 1996, November 27, 1996, November 5, 1999, and March 31, 2000.

VI INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The manufacture and use of Levofloxacin Tablets and Levofloxacin Injection are not expected to result in significant environmental releases of the active ingredient or excipients, and no potential adverse environmental effects resulting from the manufacture and use of levofloxacin have been identified.

The environmental assessment dated October 26, 1998 (which was added to the supplement to NDA 20-634 filed on June 4, 1998 for uncomplicated urinary tract infection) is the most recent document addressing fate and effects information for levofloxacin. The lowest minimum inhibitory concentration (MIC) found was 0.06 mg/L for the soil bacteria, *Bacillus subrilis*. The no observed effect on concentration (NOEC) for Daphnia magna was <43 mg/L, and the NOEC for bluegill sunfish was 630 mg/L. As the MEEC resulting from this action will be well below the MIC and the NOEC for these organisms, the original conclusion, that no environmental impact is expected, is still valid.

VII-VIII NOT REQUIRED

Sections VII, Mitigation Measures, and VIII, Alternatives to the Proposed Action, are not required when there have been no adverse environmental effects identified.

IX PREPARERS

Edward Nowak, QEP, CHMM
Staff Environmental Engineer
Johnson & Johnson Pharmaceutical Research and Development, LLC
1000 U.S. Route 202 South
Raritan, New Jersey 08869-0602

Twenty-four years of environmental experience; fifteen years with the telecommunications research and development industry, eight years with the United States Environmental Protection Agency and one year with pharmaceutical research and development.

Bachelor of Science in Civil Engineering, New Jersey Institute of Technology
Master of Science in Environmental Engineering, New Jersey Institute of Technology

X CERTIFICATION

I certify that the information presented is true and accurate and complete to the best of the knowledge of the firm responsible for the preparation of the Environmental Assessment.

Date: 12/13/2002

Signature: Edward Nowak

Edward Nowak

Title: Staff Environmental Engineer

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/s/

Florian Zielinski
1/27/03 09:06:31 AM

Nancy Sager
1/28/03 03:42:15 PM

Yuan-Yuan Chiu
2/3/03 10:13:22 AM
Concurred

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

sNDA's: 20-634 (SE1-028) & 20-635 (SE1-027)
Review Number: 1
Date of Submission: 12/23/02
Information to Sponsor: Yes ( ) No (X)

Sponsor/Manufacturer:

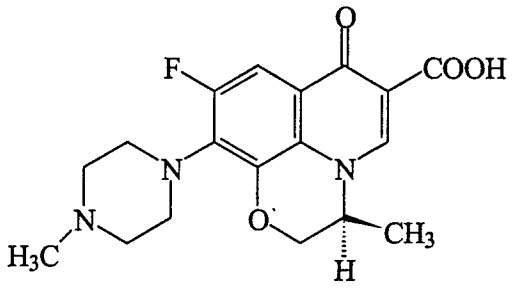
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Reviewer: Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer

Division; Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 8/18/03

Generic Name: Levofloxacin
Drug Product: Levaquin®
Chemical Name: S-(-)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl) -7-oxo-7H-pyrido [1,2,3-de] 1,4-benzoxazine-6-carboxylic acid hemihydrate
CAS #: 100986-85-4
Molecular Formula: $C_{18}H_{20}FN_3O_4 \cdot ½ H_2O$
Molecular Weight: 370.4
Molecular Structure:



· 1/2 H_2O

Relevant IND's: 36,627 & 38,368

Drug Class: Antimicrobial Fluoroquinolone

Indication: Community-Acquired Pneumonia

Clinical Formualtion: Levaquin® Tablets (750 mg); Levaquin® Injection (5 mg/ml and 25 mg/ml).

Route of Administration: Oral or intravenous

Proposed Use: 750 mg levofloxacin daily for 5 days.

Executive Summary

Recommendations:

Approvability – The NDA submission is approvable from the perspective of nonclinical pharmacology and toxicology.

Nonclinical Studies – Additional nonclinical studies are not required.

Labeling – The sponsor's proposed label is acceptable with regard to the nonclinical pharmacology and toxicology portions of the label.

Summary of Nonclinical Findings:

Nonclinical pharmacology and toxicology studies were previously submitted under IND's 36,627 and 38,368 and were sufficient to support clinical trials for the following indications for Levaquin®: acute sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, complicated skin and skin structure infections, uncomplicated skin and skin structure infections, complicated urinary tract infections, uncomplicated urinary tract infections, and acute pyelonephritis. The nonclinical data base supported the complicated skin and skin structure indication which has a 750 mg qd, 7 to 14 days dosing regimen compared to the proposed short-course community-acquired dosing regimen of 750 mg qd, for 5 days. Therefore, additional nonclinical pharmacology and toxicology studies were not required.

No additional Pharmacology/Toxicology NDA Review is provided beyond the Cover Sheet and Executive Summary.

Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Concurrence:

Kenneth Hastings, Dr. P.H., DABT
Pharmacology/Toxicology Supervisor & Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

cc:

HFD-590/CSO/S. Peacock
HFD-590/MO/L. Sacks
HFD-590/MO/R. Roca
HFD-590/Biopharm/P. Colangelo
HFD-590/Micro/S. Peacock
HFD-590/Chem/G. Holbert
HFD-590/Stat/K. Higgins

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/s/

Steve Hundley
8/22/03 11:45:39 AM
PHARMACOLOGIST

Kenneth Hastings
8/27/03 11:31:22 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-634 / SE2-028
	20-635 / SE2-027
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TABLE OF CONTENTS

Page

List of Tables **3**

1. Executive Summary **4**

1.1 Conclusions and Recommendations 4

1.2 Brief Overview of Clinical Studies 4

1.3 Statistical Issues and Findings 4

2. Introduction **5**

2.1 Overview 5

2.2 Data Sources 5

3. Statistical Evaluation **6**

3.1 Evaluation of Efficacy 6

3.1.1 Study Design and Endpoints 6

3.1.2 Study Populations 8

3.1.3 Study Withdrawals 10

3.1.4 Demographics 11

3.1.5 Efficacy Results 12

3.2 Evaluation of Safety 14

4. Findings in Special/Subgroup Populations **14**

4.1 Gender, Race and Age 14

4.2 Other Special/Subgroup Populations 16

5. Summary and Conclusions **17**

5.1 Statistical Issues and Collective Evidence 17

5.1.1 Statistical Issues 17

5.1.2 Collective Evidence 17

5.2 Conclusions and Recommendations 17

LIST OF TABLES

Page

Table 1: Patient Disposition 9
Table 2: Study Withdrawal Information: ITT Population 10
Table 3: Demographic and Baseline Characteristics: ITT Population[a] 11
Table 4: Sponsor's Clinical and Microbiologic Response Rates at 7-14 days Post-therapy 12
Table 5: Sponsor's Clinical and Microbiologic Response Rates at Post-therapy Visit 4 13
Table 6: Reviewer's Analysis of Clinical Response Rates at Post-therapy Visit 4 13
Table 7: Clinical Response Rates at Post-therapy Visit 4 by Gender 15
Table 8: Clinical Response Rates at Post-therapy Visit 4 by Age 15
Table 9: Clinical Response Rates at Post-therapy Visit 4 by Fine-risk class 16

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The clinical efficacy of levofloxacin 750 mg administered i.v. or p.o. q.d. for five days in the treatment of Community Acquired Pneumonia (CAP) was supported by one controlled study. This study demonstrated that the clinical efficacy of levofloxacin 750 mg q.d. for five days was at least as good as that of an active comparator (levofloxacin 500 mg q.d. for 10 days) assuming a non-inferiority margin (delta) of 10%.

1.2 Brief Overview of Clinical Studies

Levofloxacin is a fluoroquinolone consisting exclusively of the L-isomer of the racemate, ofloxacin. Levofloxacin and other quinolones rapidly and specifically inhibit DNA synthesis and are bactericidal. LEVAQUIN (levofloxacin) tablets and injections are approved by the FDA for the treatment of a number of bacterial infections including CAP. The recommended dose of levofloxacin in CAP is 500mg administered q.d. for 7 to 14 days. Ortho-McNeil Pharmaceutical Inc. is now seeking approval for a high-dose, short-course regimen of levofloxacin (750 mg i.v. or p.o. administered q.d. for five days) for treatment of mild to severe CAP and have submitted one pivotal, double-blind randomized, active-controlled, multi-center study (CAPSS-150) conducted in the United States. The comparator used in this study was the standard levofloxacin regimen of 500 mg q.d. for 10 days.

1.3 Statistical Issues and Findings

The population of adults, 18 years or older, with both the clinical signs and symptoms of CAP and radiographic evidence of pneumonia within 24 hours of study drug administration was studied in this multi-center, randomized, double-blind, active-control, non-inferiority study conducted in the United States. In this study, the non-inferiority of the 5-day course of levofloxacin 750 mg q.d. compared to the 10-day course of levofloxacin 500 mg q.d. (approved treatment for CAP) with a margin of 10% was demonstrated with 95% confidence in terms of clinical success rate for the ITT as well as clinically evaluable and microbiologically evaluable populations. For the ITT population, the success rates were 86.3% and 81.3% for the 5-day course and 10-day course respectively. These success rates were higher for the clinically evaluable and microbiologically evaluable populations. All subgroup/special populations analyses in this study, such as the ones based on gender, age, fine risk class, and subgroups as determined by the medical officer, all showed results generally consistent with the Intent-to-Treat population.

2. INTRODUCTION

2.1 Overview

Community Acquired Pneumonia (CAP) is an acute infection of the pulmonary paranchyma that, by definition, occurs outside the hospital setting. CAP is characterized by clinical signs and symptoms and confirmed by the presence of acute infiltrate on chest x-rays or by auscultatory findings. The leading cause of CAP is *Streptococcus pneumoniae*. Other causative organisms of CAP include the atypical pathogens *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

Levofloxacin is a fluoroquinolone consisting exclusively of the L-isomer of the racemate, ofloxacin. Levofloxacin and other quinolones rapidly and specifically inhibit DNA synthesis and are bactericidal. LEVAQUIN (levofloxacin) tablets and injections are approved by the FDA for the treatment of a number of bacterial infections including CAP. The recommended dose of levofloxacin in CAP is 500mg administered q.d. for 7 to 14 days. Ortho-McNeil Pharmaceutical Inc. is now seeking approval for a high-dose, short-course regimen of levofloxacin (750 mg i.v. or p.o. administered q.d. for five days) for treatment of mild to severe CAP and have submitted one pivotal, double-blind randomized, active-controlled, multi-center study (CAPSS-150) conducted in the United States. The comparator used in this study was the standard levofloxacin regimen of 500 mg q.d. for 10 days. The following sections contain a detailed review of this study.

2.2 Data Sources

The data sets for this study were submitted electronically at the following location:

\\Cdsesub1\N20634\S_002\2002-12-20\crt\Datasets

This reviewer found the efficacy data sets to be well organized and of good quality. Also, this reviewer did not find notable discrepancies between the results given in the text of the sponsor's study report and those obtained using submitted data sets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study CAPSS-150

3.1.1 Study Design and Endpoints

This was a multi-center, randomized, double blind, active-control, and non-inferiority study conducted in the United States. Subjects were randomized to one of the two treatment groups (levofloxacin 750 mg i.v. or p.o. q.d. or levofloxacin 500 mg i.v. or p.o. q.d.) in 1:1 ratio. Randomization was stratified by study center and by Fine Risk Score ($\leq$ 70 versus >70 but $\leq$ 130). Subjects randomized to the 750 mg dose were to receive five days of therapy and five days of placebo. Subjects randomized to the 500 mg dose were to receive 10 days of therapy.

For the purpose of this study, the definition of CAP included pneumonia in nursing home residents who had resided in a freestanding facility for < 14 days.

Subjects were to be of age 18 years or older with both the clinical signs and symptoms of CAP and radiographic evidence of pneumonia within 24 hours of study drug administration. Also subjects had to exhibit at least one of the following:

- Fever – oral temperature $\geq 38^0$C (100.4^0F);
- Hypothermia – oral temperature $\leq 35^0$C (95^0F);
- Leukocytosis (WBC > 10,000/mm^3); OR
- Bands > 10%.

Subjects had to have a Fine Risk Score $\leq$ 130 at admission.

Prior antimicrobial therapy, if taken, was either to be of duration less than 24 hours or to be of duration at least 72 hours with subject failing that therapy.

Subjects whose previous therapy was a quinolone and who failed such therapy were not eligible for study entry. Also, pregnant and nursing women were excluded from the study. Other exclusion criteria included pneumonia due to a pathogen resistant to levofloxacin, known or at high risk infection with *P. aeruginosa*, presence of neutropenia, creatnine clearance < 50 ml/min, empyema or presence of pleural fluid requiring an indwelling chest tube, pneumonia known to be due to major aspiration of gastric contents, HIV infection

with CD4 counts < 200 cells/mm^3, and seizure disorder or psychiatric condition requiring chronic use of major tranquilizers.

There were two post-therapy evaluations, Visit 3 (12-16 days after the first dose) and Visit 4 (17-21 days after first dose) and one post-study evaluation, Visit 5 (31-38 days after first dose). Clinical and microbiologic responses were assessed at post-therapy visits 3 and 4 and at post-study visit 5 based on the following definitions:

Clinical Response at Post-therapy visits

Cure: Resolution of pre-treatment abnormal clinical signs and symptoms with no further antimicrobial therapy required for CAP.

Improvement: Pre-treatment abnormal signs and symptoms subsided significantly but with incomplete resolution in a subject who required no further antimicrobial therapy for CAP.

Failure: No or incomplete response to therapy requiring additional antimicrobial therapy for CAP.

Unable to evaluate: Subject lost to follow-up.

Clinical Response at Post-study visit in subjects who were cured or improved at post-therapy visits.

Long-term cure: Resolution of clinical signs and symptoms associated with CAP and no additional antimicrobial therapy required for CAP.

Long-term improvement: Continued incomplete resolution of signs and symptoms with no deterioration during the follow-up period and no additional antimicrobial therapy required for CAP.

Relapse: Reappearance or deterioration of signs and symptoms of infection.

Unable to evaluate: subjects who received additional antimicrobial therapy for a condition other than a respiratory infection that could have been effective against the admission pathogen(s).

Microbiologic Response to infection at Post-therapy visits

Eradicated: All admission sputum and blood pathogens were eradicated or presumed eradicated without a superinfection occurring.

Persisted: Persistence or presumed persistence of one or more admission sputum or blood pathogens in the last obtained culture (on-therapy or post-therapy).

Unknown: At least one pathogen had a post-therapy microbiologic response of unknown with no pathogens persisting.

Microbiologic Response to infection at Post-study visits

Long-term Eradicated: All admission sputum and blood pathogens were eradicated with no need for additional antibacterial therapy.

Relapse: Relapse or presumed relapse of one or more admission sputum or blood pathogens in the post-study culture.

Persisted: The presence of one or more admission pathogens, or clinical relapse in a subject who had persistence of the same pathogen in sputum or blood at the post-therapy visit.

Unknown: Unknown response for at least one pathogen with no pathogens relapsing or persisting.

The definitions of **Microbiologic Response by Pathogen at post-therapy and post-study visits** were similar to the ones given above.

The primary efficacy variable was the clinical success rate (proportion cured or improved) at post-therapy visit. Protocol-specified window for the post-therapy visit (7 to 11 days after the last dose of the active study medication) was expanded to 7-14 days for the purpose of analysis. Because the duration of active treatment differed in the treatment groups, visit 3 data for levofloxacin 750 mg group which was collected 7 to 14 days after the last dose taken by subjects receiving 5 days of levofloxacin treatment was compared to visit 4 data for levofloxacin 500 mg group which was collected 7 to 14 days after the last dose taken by subjects receiving 10 days of levofloxacin treatment. The sponsor considered this analysis as the primary analysis.

Reviewer's Comment: *FDA informed the sponsor that analysis based on the data collected at the same post-therapy visit, that is visit 4, would be considered by FDA as primary analysis. The sponsor's analysis based on data collected at comparable time-points after last dose would be considered supportive.*

This study was designed to demonstrate that 5-day course of levofloxacin 750 mg, q.d. was at least as effective as the 10-day course of levofloxacin 500 mg q.d. for the treatment of CAP. Sample size was based on 88% power to show that the upper bound of the two-sided 95% confidence interval for the differences in response rates (levofloxacin 500 mg minus levofloxacin 750 mg) was less than delta (a pre-defined non-inferiority limit) of 10%. Approximately 400 to 500 subjects were to be enrolled in order to provide 344 clinically evaluable subjects (172 subjects per group) assuming that the clinical success rates for both groups would be 90%.

3.1.2 Study Populations

Three subject populations were defined for the analysis of clinical and microbiological efficacy. They are:

- Intent-To-Treat (ITT) Population: All randomized subjects who took at least one dose of study drug.

- Clinically Evaluable Population: Subjects with signs and symptoms of mild to severe CAP who were not classified into any of the following categories: unconfirmed clinical diagnosis, loss to follow-up prior to post-therapy/early withdrawal evaluation for reasons other than clinical failure, deviation from protocol dosing regimen, effective concomitant therapy, inappropriate post-therapy evaluation date or other major protocol violation.

- Microbiologically Evaluable Population: Subjects in clinically evaluable population who could not be classified into any of the following categories: infection not bacteriologically proven, inappropriate baceriologic culture, post-therapy culture results not available except those unavailable due to clinical improvement (i.e. resolution of sputum production), or clinical failure, post-therapy culture was not obtained within the specified post-therapy time-window except those who were clinical failures.

Reviewer's Comment: *The sponsor considered clinically evaluable population as primary. In this review, we consider both the ITT analysis and the analysis for the clinically evaluable population as co-primary.*

This study was conducted by 70 investigators at 70 centers in the United States. A total of 530 subjects were enrolled and randomized to receive study medication: 257 were randomized to receive levofloxacin 750 mg q.d. for five days and 273 to receive levofloxacin 500 mg q.d. for 10 days. One subject in each group received no study medication. These two subjects were not included in the ITT population. Patient disposition is shown in the following table.

Table 1: Patient Disposition

Population	Levofloxacin 750mg q.d. for 5 days	Levofloxacin 500mg q.d. for 10 days
Randomized	257	273
ITT(received study medication)	256	272
Clinically Evaluable: Post-therapy[1]	198	192
Clinically Evaluable: Visit 4	193	192
Microbiologically Evaluable:Posttherapy[1]	103	92
Microbiologically Evaluable: Visit 4	98	92

[1]: visit that occurred 7-14 days after the last dose of study medication.

3.1.3 Study Withdrawals

The treatment groups were comparable with respect to reasons for withdrawal from study prior to completion. Of the 256 ITT subjects in the 750mg group, 219 completed therapy, 34 discontinued therapy prematurely, and 3 were lost to follow-up. Of the 272 ITT subjects in the 500mg group, 218 completed therapy, 48 discontinued therapy prematurely and 6 were lost to follow-up. Subjects lost to follow-up were classified neither as having completed therapy nor as having withdrawn early from therapy on the CRF. The reasons for early withdrawal are summarized in the following table, the most common reason being adverse events in both treatment groups. "Other" reasons for early discontinuation included: decision of the attending physician, failure to meet inclusion criteria, initiation of prohibited concomitant therapy, wrong study medication kit used, lack of compliance, and incarceration.

Table 2: Study Withdrawal Information: ITT Population

Subject Disposition	Levofloxacin 750mg q.d. for 5 days (N=256)		Levofloxacin 500mg q.d. for 10 days (N=272)	
	n	%	n	%
Total Completing Therapy	219	85.5	218	80.1
Total who withdrew early from Therapy	34	13.3	48	17.6
Total Lost to follow-up	3	1.2	6	2.2
Reasons for Early Withdrawal				
Adverse Event	16	6.3	21	7.7
Renal Insufficiency	0	0.0	1	0.4
Subject Choice	3	1.2	4	1.5
Clinical Failure	3	1.2	2	0.7
Other	12	4.7	20	7.4

3.1.4 Demographics

The demographic and baseline characteristics of the ITT population are presented in the following table. The mean age for all subjects was 54.2 years with a range of 18 to 89 years. More than half (58.7%) of the subjects were men and the majority of the subjects were Caucasian (70.3%). At the study enrollment, 304 (57.6%) were categorized as Fine Risk class I/II (Fine Risk Score $\leq$ 70, Stratum II) with the mean Fine Risk Score of 44.3 and range of 8 to 70 at baseline. The remaining 224 were categorized as Class III/IV (Fine Risk Score > 70 to $\leq$ 130, Stratum I) with the mean Fine Risk Score of 91.0 and range of 71 to 149 at baseline. Five subjects in the 500mg group who had Fine Risk Scores > 130 at entry were included in Stratum I. The ITT subjects consisted of three approximately equal-sized categories of smoking history: 31.4% were non-smokers, 32.8 % were ex-smokers and 35.6% were smokers. The majority of subjects (83.1%) had no history of alcoholism.

The two treatment groups were comparable at baseline with regard to demographic characteristics, weight, height, and smoking and alcohol abuse histories. The proportion of subjects in Fine Risk Class III/IV (Fine Risk Score > 70 to $\leq$ 130, Stratum I) was higher in the 500mg group (45.2%) than in the 750mg group (39.5%). This was also the case for the clinically evaluable population.

Table 3: Demographic and Baseline Characteristics: ITT Population[a]

	Levofloxacin 750mg N=256		Levofloxacin 500mg N=272		Total N=528	
	n	%	n	%	n	%
Sex						
Male	148	57.8	162	59.6	310	58.7
Female	108	42.2	110	40.4	218	41.3
Race						
Caucasian	179	69.9	183	67.3	362	68.6
Black	51	19.9	64	23.5	115	21.8
Asian	4	1.6	3	1.1	7	1.3
Hispanic	19	7.4	21	7.7	40	7.6
Other	3	1.2	1	0.4	4	0.8
Age						
$\leq$ 45	94	36.7	85	31.3	179	33.9
46-64	82	32.0	90	33.1	172	32.6
$\geq$ 65	80	31.3	97	35.7	177	33.5
Fine Risk Class						
I/II	155	60.5	149	54.8	304	57.6
III/IV	101	39.5	123	45.2	224	42.4

[a]: information in this table is extracted from Sponsor's Section 4.1, Table 3.

3.1.5 Efficacy Results

The primary efficacy variable was the clinical success rate (proportion cured or improved) at post-therapy visit. Protocol-specified window for the post-therapy visit (7 to 11 days after the last dose of the active study medication) was expanded to 7-14 days for the purpose of analysis. Because the duration of active treatment differed in the treatment groups, visit 3 data for levofloxacin 750 mg group which was collected 7 to 14 days after the last dose taken by subjects receiving 5 days of levofloxacin treatment was compared with visit 4 data for levofloxacin 500 mg group which was collected 7 to 14 days after the last dose taken by subjects receiving 10 days of levofloxacin treatment. The sponsor considered this analysis as primary analysis.

Reviewer's Comment: *In this review, ITT analysis based on the data collected at the same post-therapy visit, that is visit 4, would be considered as primary analysis. The sponsor's analysis based on data collected at comparable time-points after last dose for ITT and clinically evaluable populations would be considered supportive. The sponsor's results are summarized in the following tables. Table 4 summarizes the efficacy analysis results at the post-therapy visit that occurred 7 to 14 days after the last dose of active medication, and Table 5 summarizes the efficacy analysis results at the post-therapy visit 4.*

Table 4: Sponsor's Clinical and Microbiologic Response Rates at 7-14 days Post-therapy

Analysis Population	Levofloxacin 750mg q.d. for 5 days (N=256)		Levofloxacin 500mg q.d. for 10 days (N=272)		95% Confidence Interval [a]
Clinical Success Rate	n / N	%	n / N	%	
ITT	224/256	87.5	221/271	81.3	(-12.6, 0.1)
Clinically Evaluable	183/198	92.4	175/192	91.1	(-7.0, 4.4)
Microbiologically Evaluable	97/103	94.2	87/92	94.6	(-6.6, 7.4)
Microbiologic Eradication Rate					
Microbiologically Evaluable	96/103	93.2	85/92	92.4	(-8.6, 7.0)

[a]: Two-sided 95% confidence interval (with Yates' continuity correction) around the difference (levofloxacin 500mg minus levofloxacin 750mg).

Table 5: Sponsor's Clinical and Microbiologic Response Rates at Post-therapy Visit 4

Analysis Population	Levofloxacin 750mg q.d. for 5 days (N=256)		Levofloxacin 500mg q.d. for 10 days (N=272)		95% Confidence Interval [a]
Clinical Success Rate	n / N	%	n / N	%	
ITT	221/256	86.3	221/272	81.3	(-11.5, 1.4)
Clinically Evaluable	180/198	90.9	175/192	91.1	(-5.4, 5.9)
Microbiologically Evaluable	96/103	93.2	87/92	94.6	(-6.4, 9.1)
Microbiologic Eradication Rate					
Microbiologically Evaluable	91/98	92.9	85/92	92.4	(-8.4, 7.5)

[a] : Two-sided 95% confidence interval (with Yates' continuity correction) around the difference (levofloxacin 500mg minus levofloxacin 750mg).

Reviewer's Comments: *In both Tables 4 and 5, for each efficacy analysis population, the upper bound of the 95% confidence interval was less than the protocol specified delta of 10%. Thus at the protocol specified non-inferiority limit, levofloxacin 750mg for 5 days was shown to be at least as effective as (non-inferior to) levofloxacin 500mg for 10 days.*

There were 134 patients in the ITT population (55 in the levofloxacin 750 mg group and 79 in the levofloxacin 500 mg group) for whom the visit 4 data were missing. For all of these patients, visit 3 data was available. The sponsor to impute the missing visit 4 measurements used this visit 3 data. This reviewer carried out sensitivity analyses to assess the impact of missing data on the primary efficacy endpoint of clinical response at visit 4. In the following table, results for 1> are obtained assuming all missing data at visit 4 are failures and results for 2> are obtained after excluding all patients with missing visit 4 data.

Table 6: Reviewer's Analysis of Clinical Response Rates at Post-therapy Visit 4

Analysis Population	Levofloxacin 750mg q.d. for 5 days (N=256)		Levofloxacin 500mg q.d. for 10 days (N=272)		95% Confidence Interval [a]
Clinical Success Rate	n / N	%	n / N	%	
ITT 1>	196/256	76.6	191/272	70.2	(-14.2, 1.6)
2>	196/201	97.5	191/193	99.0	(-1.6, 4.5)
Clinically Evaluable 1>	175/198	88.4	175/192	91.1	(-3.8, 9.3)
2>	175/180	97.2	175/177	98.9	(-1.8, 5.1)
Microbiologically Evaluable 1>	92/103	89.3	87/92	94.6	(-3.3, 13.8)
2>	92/94	97.9	87/88	98.9	(-2.7, 4.7)

[a] : Two-sided 95% confidence interval (with Yates' continuity correction) around the difference (levofloxacin 500mg minus levofloxacin 750mg).

***Reviewer's Comment**: The results of the sensitivity analyses in Table 6 are generally consistent with the results sponsor's results in Table 5. Thus at the protocol specified non-inferiority limit of 10%, levofloxacin 750mg for 5 days was shown to be at least as effective as (non-inferior to) levofloxacin 500mg for 10 days.*

Due to small sample sizes, information on eradication rates by pathogens is not reported in this review. For information on eradication rates by pathogen, please refer to the microbiological review (by Susan Peacock, PharmD).

3.2 Evaluation of Safety

One hundred forty-eight (57.8%) of the 256 safety-evaluable subjects who received levofloxacin 750 mg and 158 (59.6%) of the 265 safety-evaluable subjects who received levofloxacin 500 mg experienced at least one treatment-emergent adverse event beginning up to 14 days after the last dose of study medication. The 95% CI around the difference was (-6.8, 10.5), indicating that the overall rates of adverse events did not differ significantly between the two treatment groups.

For a summary of results with respect to safety parameters, and general discussion of safety of this drug, please refer to the clinical review (of Dr. Leonard Sacks).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

For all analyses in this section, visit 3 data is used to impute missing visit 4 data. Due to small sample sizes, inferences, if any, should be drawn with caution from these analyses.

Majority (70.3%) of subjects in this study was Caucasian and therefore the race differences, if any, can not be assessed using this data.

In this study, more than half (58.7%) of the subjects were men. The following table summarizes the results for gender based subgroups. The results are generally consistent with those in Table 6 for the entire population.

Table 7: Clinical Response Rates at Post-therapy Visit 4 by Gender

Gender Subgroup	Levofloxacin 750mg q.d. for 5 days (N=256)		Levofloxacin 500mg q.d. for 10 days (N=272)		95% Confidence Interval [a]
Male	n/N	%	n/N	%	
ITT	126/148	85.1	126/162	77.8	(-16.6, 1.9)
Clinically Evaluable	95/107	88.8	98/113	86.7	(-11.6, 7.5)
Microbiologically Evaluable	48/53	90.6	50/54	92.6	(-10.4, 14.4)
Female					
ITT	95/108	88.0	95/110	86.4	(-11.4, 8.2)
Clinically Evaluable	80/86	93.0	77/79	97.5	(-3.2, 12.1)
Microbiologically Evaluable	43/45	95.6	37/38	97.4	(-6.1, 9.7)

[a]: Two-sided 95% confidence interval (with continuity correction) around the difference (levofloxacin 500mg minus levofloxacin 750mg).

This study was conducted in the population of adults and the patient age represented in the ITT population ranged from 18 to 89 years. The following table summarizes the results for age based subgroups. Although, no conclusions can be drawn, the results for the subgroup of patients ≥ 65 years are inconsistent with other age subgroups and the overall population. For this subgroup, clinical response rates for the levofloxacin 500 mg for 10 days arm were higher than for the levofloxacin 750mg for 5 days arm. The upper bound of 95% confidence intervals for this age group exceeded the non-inferiority margin of 10% for ITT as well as clinically and microbiologically evaluable populations.

Table 8: Clinical Response Rates at Post-therapy Visit 4 by Age

Age Subgroup	Levofloxacin 750mg (N=256)		Levofloxacin 500mg (N=272)		95% Confidence Interval [a]
≤ 45 years	n/N	%	n/N	%	
ITT	85/94	90.4	67/85	78.8	(-23.2, .05)
Clinically Evaluable	64/68	94.1	53/57	93.0	(-9.8, 7.5)
Microbiologically Evaluable	38/40	95	33/35	94.3	(-10.9, 9.5)
46-64 years					
ITT	73/82	89.0	75/90	83.3	(-17.1, 5.7)
Clinically Evaluable	59/64	92.2	61/68	89.7	(-13.8, 8.8)
Microbiologically Evaluable	27/28	96.4	39/40	97.5	(-7.3, 9.5)
≥ 65 years					
ITT	63/80	78.8	79/97	81.4	(-10.3, 15.7)
Clinically Evaluable	52/61	85.2	61/67	91.0	(-7.0, 18.6)
Microbiologically Evaluable	26/30	86.7	15/17	88.2	(-18.0. 21.1)

[a]: Two-sided 95% confidence interval (with continuity correction) around the difference (levofloxacin 500mg minus levofloxacin 750mg).

4.2 Other Special/Subgroup Populations

The following table shows the analyses for the subgroups based on fine-risk class for clinically evaluable population. Although, the data did not show statistically significant treatment by fine-risk class interaction (p-value > 0.3), higher success rate was observed for levofloxacin 500mg group in the Fine Risk class I/II, where as in the Fine Risk class III/IV, Levofloxcin 750mg group had higher success rate. The 95% confidence intervals are very wide due to small sample sizes and can not be used meaningfully for statistical inference.

Table 9: Clinical Response Rates at Post-therapy Visit 4 by Fine-risk class

Gender Subgroup	Levofloxacin 750mg q.d. for 5 days (N=256)		Levofloxacin 500mg q.d. for 10 days (N=272)		95% Confidence Interval [a]
	n / N	%	n / N	%	
Fine-risk class III/IV	66/76	86.8	73/86	84.9	(-13.9, 10.0)
Fine-risk class I/II	114/122	93.4	102/106	96.2	(-3.8, 9.4)
Total	180/198	90.9	175/192	91.1	(-5.4, 5.9)

[a]: Two-sided 95% confidence interval (with continuity correction) around the difference (levofloxacin 500mg minus levofloxacin 750mg).

The sponsor presented analyses for subgroups based on admission pathogen as well. All these analyses showed results that were consistent with the primary analysis, and showed that levofloxacin 750mg for 5 days regimen was at least as effective as levofloxacin 500mg for 10 days regimen (that is currently approved) for the treatment of CAP. The reader is refered to microbiology review by Susan Peacock, PhramD.

The medical officer reviewing the application was concerned about the inclusion of certain patients who violated at least one of the criteria for the diagnosis of CAP. When these patients were excluded from the ITT population, the results for the population of remaining patients were consistent with the results in Tables 5 and 6 for the entire population. For the details of this analysis, please refer to the clinical review of Dr. Leonard Sacks.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

The non-inferiority margin of 10% was determined based on clinical judgment regarding the acceptable loss in the success rate from existing therapy $delta_2$, because it is currently thought that the treatment effect of the active control over placebo $delta_1$ is larger than 10%. Note that in the future a better understanding of the magnitude of $delta_1$ may be required.

5.1.2 Collective Evidence

This document contains statistical review of one pivotal study. The sponsor's application contained a supporting open-label, noncomparative, trial (CAPSS-171) using the proposed 750 mg q.d. for five days regimen, and supporting data from previously approved applications for levofloxacin 750mg q.d. for 7 to 15 days in the treatment of nosocomial pneumonia (CAPSS-117) and for levofloxacin 500mg q.d. for 7 to 14 days in the treatment of serious CAP and severe CAP.

The CAPSS-171 study was conducted in parallel with the pivotal trial enrolling subjects who did not meet some inclusion criteria of the pivotal trial and using 750mg q.d. for five days regimen. The clinical success rate in this study was 79.7% for the clinically evaluable population, which was lower than that observed in the pivotal study (90.9%). The sponsor explained the lower response rate via a discussion of confounding factors such as the advanced age of the subject population, and inclusion of subjects with renal insufficiency. For more discussion of this study and other supportive data, the reader is referred to the clinical review by Dr. Leonard Sacks.

5.2 Conclusions and Recommendations

The clinical efficacy of levofloxacin 750 mg administered i.v. or p.o. q.d. for five days in the treatment of community acquired pneumonia was supported by one controlled study. This study demonstrated that the clinical efficacy of levofloxacin 750 mg q.d. for five days was at least as good as that of an active comparator (levofloxacin 500 mg q.d. for 10 days) assuming a non-inferiority margin (delta) of 10%.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

MICROBIOLOGY REVIEW(S)

Microbiology Review

Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

NDA #: 20-634/S-028 20-635/S-027	**Reviewer:**	Susan R. Peacock
	Correspondence Date:	20 DEC 2002
	CDER Receipt Date:	23 DEC 2002
	Review Assign Date:	06 JAN 2003
	Review Completion Date:	18 AUG 2003

Sponsor:

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Contact Person:

Robyn Keown
Manager, Regulatory Affairs

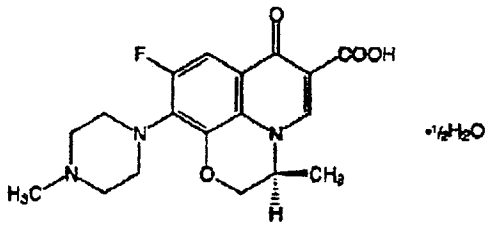
Submission Reviewed:

Efficacy Supplement for Community-Acquired Pneumonia, 750 mg q.d. for 5 days

Drug Identification:

Generic Name: levofloxacin
Trade Name: Levaquin®
Chemical Name: (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate

Chemical Structure:



Molecular Formula:	$C_{18}H_{20}FN_3O_4 \bullet ½ H_2O$
Molecular Weight:	370.38
Pharmacologic category	Fluoroquinolone antimicrobial
Dosage Form	Tablets (NDA 20-634) and Solution (20-635)
Route of Administration	Oral (NDA 20-634) and Parenteral (NDA 20-635)
Strength	750 mg
Related INDs	36,627 (tablets) and 38,638 (solution)

TABLE OF CONTENTS

Pages

Executive Summary.....3

Introduction and Background.....4

Pre-Clinical Microbiology (In Vitro).....4

In Vitro Activity of Levofloxacin Against Target Pathogens
Data from Original NDA (1990s).....4-5
Data form Literature Search (1995-2001).....5-6

Clinical Microbiology
Study Design of CAPSS-150 Pivotal Study.....6-9
Clinical Laboratory Susceptibility Tests and Methods.....9-13
Mycoplasma pneumoniae IgG/IgM Indirect Fluorescent Antibody Test System.....10-11
Chlamydia pneumoniae IgG/IgM Micro-Immunofluorescent Antibody Test.....11-12
.....12-13
Case Definitions for Atypical Pathogens.....13
Microbiology Results
In Vitro Susceptibility.....14
FDA Analysis of Microbiological Efficacy.....16-23
Microbiologic Eradication Rates by Subject.....16
Microbiologic Eradication Rates by Pathogen.....17
Microbiologic Eradication Rates by Pathogens of Interest.....18-23
Superinfections.....24
New Infectors.....25
FDA Conclusions from CAPSS-150 Study.....25

Study Design of CAPSS-171 Supportive Study
Microbiology Results
In Vitro Susceptibility.....26
FDA Analysis of Microbiological Efficacy.....27-32
Microbiologic Eradication Rates by Subject.....27
Microbiologic Eradication Rates by Pathogen.....28
Microbiologic Eradication Rates by Pathogens of Interest.....29-32

FDA Conclusions from CAPSS-171 Supportive Study.....33

Recommendations.....33

Executive Summary:

Levaquin® was approved for the indication of community-acquired pneumonia in 1996 for 500 mg tablets q.d. for a duration of 7-14 days. The sponsor is requesting a change to the labeling for levofloxacin to include a shorter course of treatment (five days) at a higher dose (750 mg once daily) in the treatment of mild to severe community-acquired pneumonia in adults. The specific organisms requested are *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Chlamydia pneumoniae,* [redacted] and *Mycoplasma pneumoniae.*

The efficacy of levofloxacin 750 mg administered orally q.d. for 5 days for the treatment of community-acquired pneumonia is supported by a clinical trial CAPSS-150. The safety data for the 750 mg 5-day regimen are derived from 26 phase 3 studies; 23 of these studies were previously completed plus the three recently completed studies CAPSS-150, CAPSS-171, and CAPSS-078.

Efficacy criteria:

1) Clinical response at Postherapy Visits 3 (Study Days 12-16) and 4 (Study Days 17-21) based on resolution of signs and symptoms observed on admission.
2) Clinical response at Poststudy Visit 5 (Days 31-38) in subjects who were cured or improved at the posttherapy visits.
3) Changes in signs and symptoms from admission to posttherapy.
4) Changes in x-ray findings from admission to posttherapy and to poststudy.
5) Microbiological outcome at posttherapy was a secondary evaluation of therapy.

The microbiologic eradication rates per pathogen seem to be higher for the 750 mg q.d. oral levofloxacin 5-day regimen treatment group than for the 500 mg q.d. oral levofloxacin 10-day regimen group. The microbiologic relapse rates were comparable at poststudy for the 750 mg and 500 mg group with a rate of 2%. The overall pathogen persistence rates were higher for the 500 mg 10-day regimen versus the 750 mg 5-day regimen.

Regarding the pathogens of interest isolated from respiratory cultures (typical pathogens), the microbiologic eradication rates at posttherapy visits were about 10% higher for the 750 mg group for *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Streptococcus pneumoniae.* However, at the poststudy visits, the microbiologic eradication rates for the 750 mg and 500 mg treatment groups were comparable for the typical pathogens. Therefore, the 750 mg dose seems to have more of an effect against the typical pathogens within the first 12-21 days of the study. By day 17-24 of the study, the effectiveness of the 500 mg 10-day and 750 mg 5-day regimens are almost equivalent. For both *H. influenzae* and *H. parainfluenzae*, there was no persistence noted for the 750 mg group. The persistence rate for both *H. influenzae* and *H. parainfluenzae* for the 500 mg treatment group was 8% and 11%, respectively. For *S. pneumoniae*, the persistence rates for the 500 mg group were also higher than those of the 750 mg treatment group. There were no microbiologic relapses noted for either treatment group for these typical respiratory pathogens.

Regarding the pathogens of interest identified by serology, the microbiologic eradication rates were 100% for [redacted] or both treatment groups. For *Chlamydia*

pneumoniae, the 500 mg 10-day regimen seemed more effective with a presumed eradication rate of 100% versus 87% for the 750 mg treatment group. However, at poststudy, the 500 mg and 750 mg treatment groups had very similar presumed eradication rates for *Chlamydia pneumoniae*. The persistence rate was much higher for the 750 mg treatment versus the 500 mg treatment regimen which had no persistence throughout posttherapy/poststudy. For *Mycoplasma pneumoniae*, the presumed eradication rates for the 750 mg and 500 mg groups were very similar throughout posttherapy and poststudy. The presumed persistence rates for the 500 mg groups were higher than the 750 group. For *C. pneumoniae* and [redacted] no microbiologic relapses were noted for either treatment group. For *Mycoplasma pneumoniae*, the microbiologic relapse rate for the 750 group was moderately higher than the relapse rate for the 500 mg group.

Introduction and Background

Levaquin® (levofloxacin) was approved for the treatment of Community-Acquired Pneumonia (CAP) in December of 1996 for 500 mg for a duration of 7-14 days. The applicant has submitted a supplement to request a change in the labeling for levofloxacin to include a shorter course of treatment (5 days) at a higher dose (750 mg once daily) in the treatment of mild to severe community-acquired pneumonia (CAP) in adults. The efficacy of levofloxacin 750 mg administered orally q.d. for 5 days for the treatment of CAP is supported by a clinical trial, CAPSS-150 "A multicenter, randomized, open label Phase 3B trial to compare the safety and efficacy of levofloxacin at 750 mg i.v. or orally q.d. for five days to that of levofoxacin at 500 mg i.v. orally q.d. for 10 days in the treatment of mild to severe CAP in adults". The proposed indication is further supported by an open-label, non-comparative, Phase 3 trial CAPSS-171 which was run in parallel with the CAPSS-150 pivotal study. Both studies involved the administration of levofloxacin 750 mg (i.v. or p.o.) q.d. for five days for the treatment of CAP in adults. The specific organisms for which coverage is requested are *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Chlamydia pneumoniae,* [redacted] and *Mycoplasma pneumoniae*. The applicant provided a literature search of levofloxacin susceptibility data (1995-2001) for these [redacted] argeted organisms, as well as susceptibility data from the CAPSS-150 pivotal study.

Preclinical Microbiology (In Vitro):

Mechanism of Action:

No new information has been submitted.

In Vitro Activity of Levofloxacin Against Target Pathogens:

Data From Original NDA (1990s)

The following data have been submitted to demonstrate that levofloxacin is active against the [redacted] ganisms associated with community-acquired pneumonia (CAP). Table 1 summarizes MIC (minimum inhibitory concentration) susceptibility data from the original NDA 20-634 for levofloxacin for five of the [redacted] quested bacterial pathogens (except *H. parainfluenzae*)

associated with CAP infections. NDA 20-634 was submitted in December 1995, therefore, data presented represents isolates collected and tested in the early 1990's.

Table 1: Antimicrobial Activity of Levofloxacin Against Organisms Associated With Community-Acquired Pneumonia: Summary Data from Microbiology Section of the Original Levofloxacin NDA

Organism	No. of Isolates	MIC Range (µg/mL)	MIC_{50} Range (µg/mL)	Median MIC_{50} (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)
C. pneumoniae	11	0.125-0.5	0.25	NA	0.5	0.5
H. influenzae	80	0.015 – 0.5	≤0.025-0.03	0.03	≤0.025-0.03	0.03
M. pneumoniae	64	0.25 – 0.5	NA	NA	0.5	0.5
S. pneumoniae	64	0.25 – 12.5	0.5 – 1	0.78	0.5 – 2	1.56
Adapted from Table 2 of CAPSS-150 Study Report						

The table above shows that in the early 1990's *C. pneumoniae* ← *I. influenzae*, and *M. pneumoniae* had median MIC_{90} values (µg/mL) of 0.5, 0.03, 0.125, and 0.5 respectively. The levofloxacin median MIC_{90} value for *S. pneumoniae* was 1.56 µg/mL, which was below the susceptible breakpoint for levofloxacin (2 µg/mL).

Data From Literature Search (1995-2001)

A literature search was conducted by the sponsor to identify publications from 1995-2001 reporting susceptibility data for levofloxacin when tested against any of the six targeted microorganisms. The purpose of this literature search was to determine whether the susceptibility data observed in the original NDA references (Table 1) were comparable to those from a more recent comprehensive literature review. Table 2 below summarizes the antimicrobial activity of levofloxacin to the targeted species.

Table 2: Antimicrobial Activity of Levofloxacin Against Organisms Associated with Community Acquired Pneumonia (Literature Review 1995-2001)

Organism	No. of Isolates	MIC Range All Isolates (µg/mL)	MIC_{50} Range (µg/mL)	Median MIC_{50} (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)
C. pneumoniae	45	0.125 – 1	0.25 – 0.5	0.5	0.5 – 1	1
H. influenzae	17, 604	≤0.004 – 8	0.015 – 0.5	0.03	0.015 – 0.6	0.03
H. parainfluenzae	56	0.03 – 2	0.03	0.03	0.25	0.25
M. pneumoniae	235	0.031 – 8	0.25 – 0.5	0.5	0.5 – 1	0.5
S. pneumoniae	48, 601	0.001 – 64	0.5 – 1	0.5	0.5 – 2	1
Adapted from Table 2 of CAPSS-150 Study Report						

The comprehensive literature review demonstrated that the median MIC_{90} values for levofloxacin were below the respective susceptible breakpoints for a — rgeted pathogens: *S.*

pneumoniae. [redacted] *H. influenzae, H. parainfluenzae, C. pneumoniae, and M. pneumoniae.* The MIC_{90} values were also about the same as those from the original NDA (Table 1).

Clinical Microbiology

Study Design of CAPSS-150

This pivotal, multicenter, randomized, double-blind, Phase 3B study was designed to compare the safety and efficacy of levofloxacin 750 mg once daily for five days versus levofloxacin 500 mg once daily for ten days in the treatment of mild to severe community-acquired pneumonia. This study was conducted in the United States.

Efficacy was evaluated at two posttherapy visits and one poststudy visit for all subjects:

- Admission Visit 1, Study Day 1
- On-Therapy Visit 2, Study Day 3
- Posttherapy Visit 3, Study Days 12-16
- Posttherapy Visit 4, Study Days 17-21
- Poststudy Visit 5, Study Days 31-38

The primary efficacy variable for the study was the clinical response in subjects evaluable for clinical efficacy. Clinical response was to be evaluated by the investigator by comparing the signs and symptoms present at posttherapy visits with those present at admission. Subjects with a successful clinical outcome at the posttherapy visits were to return for the post study visit. Secondary efficacy variables were:
1) Post-therapy microbiologic response by subject's infection
2) Post-therapy microbiologic response by admission pathogen
3) Changes in signs and symptoms from admission to post-therapy and changes in x-ray findings from admission to post-therapy and to post-study
4) Poststudy clinical and microbiologic responses of subjects who were cured or improved at the posttherapy visit and returned or had a telephone contact at poststudy.

Entry Criteria:

- Men and women 18 years of age or older
- Clinical diagnosis of Community-acquired Pneumonia based on the following evidence:
  - Clinical signs and symptoms of a lower respiratory tract infection
  - Radiographic evidence of pneumonia (chest x-ray with acute infiltrate consistent with pneumonia determined by a radiologist) within 24 hours of study drug administration
  - Fever, hypothermia, leukocytosis or bands (early forms of white blood cells) >10%
  - Fine Risk Score of 130 or less

Exclusion Criteria:

- Clinical infections due to organisms known to be resistant to levofloxacin
- Pneumonia acquired in a hospital
- Diagnosis of cystic fibrosis, bronchiectasis, or lung abscess
- Chronic use of > 20 mg/day of prednisone or equivalent dose of other corticosteroids
- Neutropenia
- Calculated creatinine clearance < 50 mL/min
- Documented infection with HIV with CD4 counts $\leq$200 cells/mm^3
- Pregnancy, nursing, or meningitis

Microbiologic outcomes were to be rendered for subjects who had a pathogen identified at admission. Microbiologic eradication was to be assessed at the posttherapy (Visits 3/4) and poststudy (Visit 5) visits. For pathogens identified through serology or urine antigen testing, the microbiologic response at posttherapy and poststudy was to be based upon the clinical response at the corresponding visit.

Posttherapy Microbiologic Response by Subject's Infection
Each subject's infection (due to one or more pathogens) was to be assigned a microbiologic response at the posttherapy (or early termination) visits. Posttherapy microbiologic response was to be assigned based on the culture results for all pathogens isolated at admission and, when applicable, upon the subject's clinical response, as follows:

- **Eradicated:** All admission sputum and blood pathogens were eradicated or presumed eradicated without a superinfection occurring.
- **Persisted:** Persistence or presumed persistence of one or more admission sputum or blood pathogens in the last obtained culture (on-therapy or posttherapy).
- **Unknown:** At least one pathogen had a posttherapy microbiologic response of unknown with no pathogens persisting.

Poststudy Microbiologic Response by Subject's Infection
For subjects cured or improved at both posttherapy visits, poststudy microbiologic response was to be assigned based on the poststudy culture results for all pathogens isolated at admission and, when applicable, upon the subject's clinical response, as follows:

- **Long-Term Eradication:** All admission sputum and blood pathogens were eradicated with no need for additional antibacterial therapy.
- **Microbiologic Relapse:** Relapse or presumed relapse of one or more admission sputum or blood pathogens in the poststudy culture.
- **Persisted:** The presence of one or more admission pathogens, or clinical relapse in a subject who had persistence of the same pathogen in sputum or blood at the posttherapy visit.
- **Unknown:** Unknown response for at least one pathogen with no pathogens relapsing or persisting.

Organisms that were initially susceptible at admission but subsequently acquired resistance were to be identified. The emergence of a new pathogen in the posttherapy culture that had not been isolated at admission was to be listed.

Posttherapy Microbiologic Response by Pathogen
The microbiologic response for respiratory and blood pathogens isolated at admission was to be determined at the posttherapy (or early termination) visit and at the poststudy visit. For test of cure, each respiratory pathogen isolated at admission was to be assigned to one of the following microbiologic response categories based on the posttherapy culture results and the subject's clinical response:

- **Eradicated:** Absence of the admission pathogen(s) in a posttherapy sputum or blood culture obtained in the absence of potentially effective systemic antibacterials.
- **Presumed Eradicated**: Presumed absence of the admission pathogen at posttherapy for subjects deemed clinical successes for whom no respiratory material for test-of-cure culture was available. Blood cultures were never to be presumed eradicated.
- **Persisted:** Continued presence of the admission pathogen in the posttherapy sputum or blood culture.
- **Presumed Persisted**: Presumed presence of the admission pathogen at posttherapy for subjects with clinical failure for whom no test-of-cure culture was taken or a negative test-of-cure culture was obtained in the presence of potentially effective systemic antibacterials.
- **Persisted with Acquisition of Resistance:** Continued presence of the admission sputum or blood pathogen in the posttherapy culture with documented acquisition of resistance.
- **Unknown:** No test-of-cure culture available, because the subject was lost to follow-up or withdrew from therapy prematurely, or a negative culture obtained in the presence of potentially effective systemic antibacterials (except as noted above for presumed persisted).

Poststudy Microbiologic Response by Pathogen
For assessment of microbiologic response at poststudy in subjects who were cured or improved at the posttherapy visits, each respiratory and blood pathogen isolated at admission was to be assigned to one of the following microbiologic response categories based on the poststudy culture results and the subject's clinical response:

- **Eradicated:** Continued absence or presumed absence of the admission sputum or blood pathogen at the poststudy evaluation.
- **Microbiologic Relapse:** Reappearance of an organism in sputum or blood identical to that isolated at admission, isolated from the original site of the infection at the poststudy visit following eradication of the original pathogen at the posttherapy evaluation.
- **Presumed Microbiologic Relapse:** Presumed reappearance of the admission pathogen in sputum or blood at poststudy for subjects who developed signs and symptoms of an infection (at the same site[s] as the admission infection) necessitating new antibacterial therapy (clinical relapse) but for whom no culture results were available prior to antibacterial treatment of the clinical relapse.

- **Unknown:** No culture results available (except as noted above for presumed microbiologic relapse) or a negative culture was obtained while on or following a course of potentially effective antibacterials administered between the posttherapy and poststudy visits for reasons other than infection at the original site.

Organisms that were initially susceptible at admission but subsequently acquired resistance (as determined from posttherapy or poststudy culture results) were to be identified and listed.

Microbiologic Response by Pathogens Identified by Serology or Urine Antigens at Posttherapy and Poststudy

Serology (done at admission and either posttherapy [for early withdrawals] or poststudy) and urine antigens (done at admission) were only to be used to determine whether certain atypical pathogens (i.e., *L. pneumophila, C. pneumoniae,* and *M. pneumoniae* via serology, [redacted] a urine antigen) were present at admission. Consequently, for pathogens identified via serology or urine antigens, the microbiologic response at posttherapy had to be based on the clinical response at posttherapy and was to be determined as follows:

Clinical Response	Effective Concomitant Therapy	Serologic/Antigen Microbiologic Response
Clinical Cure/Improvement	No	Presumed Eradicated
Clinical Cure/Improvement	Yes	Unknown
Clinical Failure	Yes, No	Presumed Persisted
Unable to Evaluate	Yes, No	Unknown

The microbiologic response at poststudy for pathogens identified via serology or urine antigens was to be determined in an analogous manner, as follows:

Clinical Response	Effective Concomitant Therapy	Microbiologic Response
Clinical Cure/Improvement	No	Presumed Eradicated
Clinical Cure/Improvement	Yes (for pneumonia)	Presumed Relapse
Clinical Cure/Improvement	Yes (for indication other than pneumonia)	Unknown
Clinical Relapse	Yes, No	Presumed Relapse
Unable to Evaluate	No	Unknown
Unable to Evaluate	Yes (for pneumonia)	Presumed Relapse
Unable to Evaluate	Yes (for indication other than pneumonia)	Unknown

Clinical Laboratory Susceptibility Tests and Methods

Microbiological data were obtained from serology, blood and respiratory secretion cultures, and urine antigens. All clinical isolates were sent to the [redacted] for confirmation of identification and for susceptibility testing. The studies were conducted according to NCCLS (National Committee for Clinical Laboratory Standards) guidelines. The MIC susceptibility data was determined by broth microdilution assays for

Haemophilus influenzae, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*. The MIC range for testing levofloxacin was ≤1 to ≥8 µg/ml (see Table 3).

Table 3: Antimicrobial Activity of Levofloxacin Against Clinical Isolates from Study CAPSS-150

Organism	No. of Isolates	MIC Range (µg/ml)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
H. influenzae	29	0.015-0.06	0.015	0.03
H. parainfluenzae	24	0.015 – 0.5	0.03	0.125
S. pneumoniae	56	0.25 – 2	1	1
Adapted from Table 4 of CAPSS-150 Study report				

Serologic testing was used to determine the clinical response and microbiologic eradication of the atypical pathogens *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. The serologic tests conducted are experimental procedures and their usefulness in measuring drug efficacy is not known. These procedures were conducted by and are described below:

- ***Mycoplasma pneumoniae* IgG/IgM Antibody Test System by Zeus Scientific, Inc.**

  Serological testing for *M. pneumoniae* antibody was performed using an indirect fluorescent antibody (IFA) system. These kits are pre-standardized to detect the presence of circulating IgG or IgM antibody to *M. pneumoniae* in human serum. A particulate slurry of *M. pneumoniae* antigenic substrate is affixed to a multi-well microscope slide. Human serum to be tested is incubated with this substrate; and antibody, if present, can be observed after staining with a fluorescein-labeled, goat anti-human IgG or IgM conjugate. The presence of bright, apple-green fluorescence in the particulate slurry on the slide under a UV light microscope indicates a positive reaction. This test system is for *in vitro* diagnostic use. Positive and negative controls e also used as well as an assayed independent control with a specified titer. The following data regarding the performance characteristics of this assay were obtained from a study performed b using human sera from patients with *M. pneumoniae* infection (defined as illness with fever, pneumonitis via X-ray, normal sputum flora, and negative ters that responded to erythromycin therapy, or history of previous exposure):

	Specificity	Predictive Value	
		POS	NEG
Complement Fixation	95.3%	71.4%	99.2%
	94.4%	68.2%	94.4%
	97.6%	85%	96%
Reference Ranges:	Negative = < 1:16 for IgM	Negative = < 1:128 for IgG	

Comment: *M. pneumoniae infection may be diagnosed by isolation of the pathogen in culture but it requires several weeks and is not widely available, so various serologic approaches have been employed. The IFA is one of the oldest serologic procedures used however it has some shortcomings with regard to cross-reactivity between M. pneumoniae and M. genitalium and subjectivity when reading the slides. The positive predictive value for this test is also quite low. (The information above was taken from the June 6, 2003, submission from J&J regarding the serology test kits used for serology testing).*

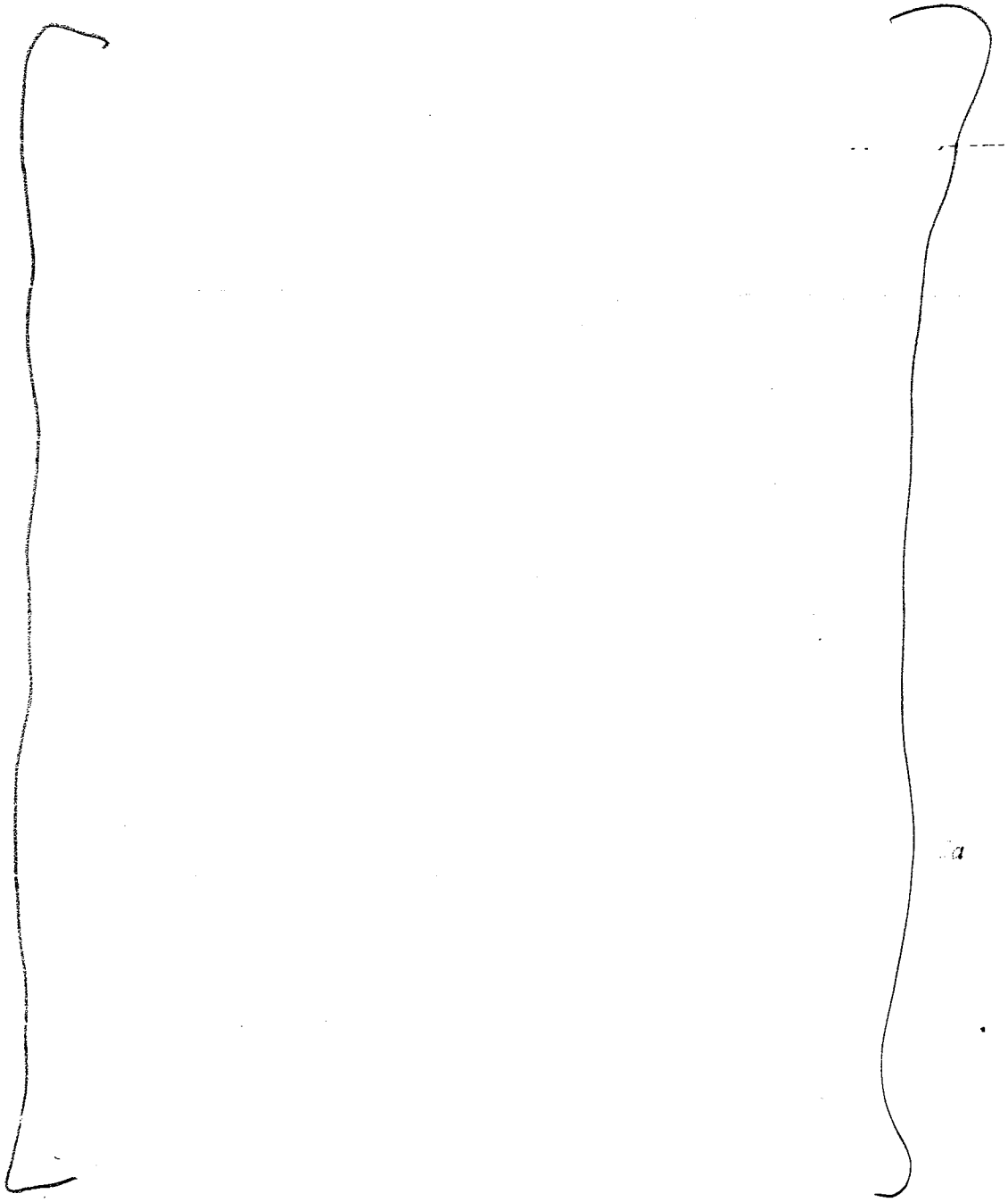
- ***Chlamydia pneumoniae* IgG/IgM Micro-Immunofluorescent Antibody (MIF) Test by**

This test is intended for the qualitative detection and semi-quantitation of human serum IgG and IgM antibodies to *C. pneumoniae*. This assay is indicated for testing pneumonia patients as an aid in diagnosing community-acquired pneumonia caused by *C. pneumoniae*. The *C. pneumoniae* MIF is approved for investigational use only within the United States. There is no *C. pneumoniae* reagent kit that will provide IgG, IgM, and IgA titers to *C. pneumoniae* that is FDA-approved. [redacted] *C. pneumoniae* MIF assay uses one strain of *C. pneumoniae*, two strains of *C. psittaci* and eight serotyopes (D-K) of *C. trachomatis*. The Micro-IF for *C. pneumoniae* (TWAR) is performed by using the purified chlamydial elementary bodies as the antigen. These chlamydial elementary bodies are treated with a proprietary process to remove interfering LPS (lipopolysaccharides) and diluted in 3% yolk sac to add contrast to the background. The antigen is placed as dots on a slide, air-dried and fixed on the slides with acetone. When testing patient serum, serial dilutions of the serum are placed on the antigen dots. The slide is then placed in a moist chamber for incubation, put through a series of gentle saline washes, and dried. A fluorescein-conjugated anti-human globulin (IgG or IgM as required) is then placed on the slide. After washing and drying, the slides are read for fluorescence using a UV microscope. The last dilution giving bright fluorescence clearly associated with the antigen dots is read as the titer. Positive and negative serum controls are used, as well as a yolk sac control and an external control. There is no commercial, assayed external control for this test nor is there an interlaboratory proficiency survey available to compare one laboratory to another. The interpretation of the *Chlamydia pneumoniae* (TWAR) antibody titer is based on a four-fold or greater change in antibody titer over time (at least 4 weeks).

Comment: *Chlamydia pneumonia MIF test is the gold standard but it is technically demanding and cross reactions can occur with C. trachomatis and with those patients having circulating rheumatoid factor. It is also a very subjective test to read. Also, about 25-45% of adults should have a low titer IgG antibody to TWAR from previous infection with the respiratory disease. This information is supported by the following studies:*

1. *Olga Tapia, et al., 2002. Inclusion Fluorescent-Antibody Test as a Screening Assay for Detection of Antibodies to Chlamydia pneumoniae, Clinical and Diagnostic Laboratory Immunology, 9 (3):562-567.*

2. *Cho-chou Kuo et. al, 1995. Chlamydia pneumoniae (TWAR), Clinical Microbiology Reviews, p. 451-461.*
3. *Peeling RW, Wang SP, Grayston JT, Blasi F, Boman J, Clad A et al. Chlamydia pneumoniae serology: interlaboratory variation in microimmunofluorescence assay results. J Infect Dis 2000;181 Suppl 3:S426-S429.*



[redacted]

Case Definitions for Atypical Pathogens:

[redacted]

Chlamydia pneumoniae-Respiratory signs and symptoms compatible with pneumonia, in association with one or more of the following:

- A fourfold increase or decrease in the microimmunofluorescence IgM titer at Visit 3-Posttherapy (Study Day 12-16) and Visit 5-Poststudy (Study day 31-38).
- A fourfold increase or decrease in the microimmunofluorescence IgG titer at Visit 3-Posttherapy (Study Day 12-16) and Visit 5-Poststudy (Study day 31-38).
- A positive culture at admission for *Chlamydia pneumoniae.*

Mycoplasma pneumoniae- Clinical and radiologic evidence of pneumonia in association with one of more of the following:

- A single IgM ELISA >1:16 or a fourfold increase or decrease at Visit 3-Posttherapy (Study day 12-16) and Visit 5-Poststudy (Study Day 31-38).

- A single IgG ELISA >1:128 or a fourfold increase or decrease at Visit 3-Posttherapy (Study day 12-16) and Visit 5-Poststudy (Study Day 31-38).

Microbiology Results

In Vitro Susceptibility

The table below (Table 4) includes a summary of the *in vitro* susceptibility of all typical respiratory and blood pathogens isolated from the intent-to-treat (ITT) population. A total of 189 admission pathogens were isolated. Of those, 87 pathogens were isolated from 68 subjects in the levofloxacin 750 mg treatment group and 102 pathogens were isolated from 70 subjects in the levofloxacin 500 mg group. Of the pathogens with known susceptibilities, 73/73 isolated from subjects in the 750 mg group and 84/85 isolated from subjects in the 500 mg group were susceptible to levofloxacin. One pathogen isolated from a subject in the 500 mg group had intermediate susceptibility but none of the pathogens isolated and tested were resistant to levofloxacin.

Table 4: In Vitro Susceptibility of Respiratory and Blood Pathogens Identified at Admission: Intent-to-Treat Population (Study CAPSS-150)

	Pathogens [a]	
	Levofloxacin 750 mg q.d. 5-day Regimen	Levofloxacin 500 mg q.d. 10-day Regimen
Susceptibility of Pathogen	N (%)[b]	N (%)[b]
Susceptible	73 (100.0)	84 (98.8)
Intermediate	0 (0.0)	1 (1.2)
Unknown Susceptibility	14	17
Total No. Pathogens	87	102

[a] Pathogens were identified from 68 subjects in the levofloxacin 750 mg q.d. group and 70 subjects in the comparator group.
[b] Percentages were based on the total numbers of pathogens with known susceptibilities to the specified drug.
**Adapted from Table 17 of CAPSS-150 Study Report*

The medical officer was concerned that the ITT population identified above (Table 4) included patients that did not have community-acquired pneumonia of bacterial etiology. Thus, the following patients were excluded from the clinically/microbiologically evaluable population:

11 patients with >10% bands (all also had abnormal WBC counts)

9018	47025	75003	78034
38008	61006	75008	133012
38023	66003	78027	

Altogether there were 104 patients with normal temperature (>35°C and <38°C), normal WBC (>3.8 and <10.7) and bands <10% (SUBNUM below) at the admission visit. These (tabulated below) were excluded from the medical reviewer's clinically evaluable population.

*3001		22003	39001	61003	78036	99007	134002
3002	10001	23001	39003	62003	78037	99008	134009
3003	10003	23003	39004	62005	78040	99009	134010
3005	10005	23007	39006	63001	79009	102001	134011
4002	10006	23008	39007	64002	83007	105001	134017
6024	11002	23016	39010	66001	87001	106001	135001
7002	14001	23020	39011	66002	89004	106002	136001
7003	15003	23021	41003	69001	89006	108004	
7005	15004	27003	41004	69002	91017	124002	
8001	15008	31001	46001	71002	91018	129003	
8002	15014	37002	46002	71008	92001	129004	
8003	16001	37007	46003	78018	92005	133002	
9005	16002	37008	47002	78020	94001	133010	
9021	16004	*38019	47014	78024	96002	133011	

*these two patients had an abnormal temperature on the "on therapy visit" and were included in the reviewer's clinically evaluable population.

The following subject numbers were excluded from the atypical pathogen population by the microbiology reviewer due to noncompliance with the case definitions as described above in the CAPSS-150 Study Report:

Chlamydia pneumoniae	*Mycoplasma pneumoniae*
38005	6008
38015	37002
47029	39003
59002	47020
63001	47026
71002	67001
71003	71008
78013	133006
85001	134005
134010	135001

FDA Analysis of Microbiological Efficacy (microbiologically evaluable population)

Microbiologic Eradication Rates by Subject's Infection:

Table 5 below demonstrates the microbiologic eradication rate by subject's infection for the posttherapy visits and the poststudy visit for the microbiologically evaluable population. The overall microbiologic eradication rate at the posttherapy visits was 95% in the levofloxacin 750 mg group and 86% in the levofloxacin 500 mg group. The overall microbiologic eradication rate (includes presumed eradication) at the poststudy visit was 83% in the levofloxacin 750 mg group and 74% in the levofloxacin 500 mg group. In addition, the microbiologic relapse rate (includes presumed relapse) for the 750 mg and 500 mg regimens was 2% and 5% respectively.

Table 5: Microbiologic Eradication Rates (by subject)

	750 mg q.d. 5-day Regimen N=105	500 mg q.d. 10-day Regimen N=96
	Visit 3	**Visit 3**
Eradicated	100 (95%)	83 (86%)
Persisted	5 (5%)	11 (11%)
Unknown	-	2 (2%)
	Visit 4	**Visit 4**
Eradicated	100 (95%)	83 (86%)
Persisted	5 (5%)	11 (11%)
Unknown	-	2 (2%)
	PostStudy	**PostStudy**
Eradicated/Presumed Eradicated	87 (83%)	79 (82%)
Microbiologic Relapse/Presumed Relapse	2 (2%)	5 (5%)
Persisted	8 (8%)	8 (8%)
Unknown	8 (8%)	4 (4%)

Microbiologic Eradication Rates by Pathogen:

Table 6 demonstrates the microbiologic eradication rate by pathogen for the posttherapy visits and the poststudy visit for the microbiologically evaluable population. The overall eradication rate (includes presumed eradicated) at the posttherapy visits was 95% for the levofloxacin 750 mg q.d. group and 88% for the levofloxacin 500 mg q.d. group. The eradication rate (includes presumed eradicated) at the poststudy visit was 89% for the 750 mg q.d. group and 79% for the 500 mg q.d. group. The persistence rates at posttherapy visits were 5% for the 750 mg group and 10% for the comparator group. The persistence rates at poststudy visits were 4% for the 750 mg group and 8% for the comparator group. The microbiologic relapse rates (includes presumed relapse) at poststudy were 2% for both the 750 mg and 500 mg regimens.

Table 6: Microbiologic Eradication Rates (by pathogen)

	750 mg q.d. 5-day Regimen N=105	500 mg q.d. 10-day Regimen N=96
	Visit 3	**Visit 3**
Eradicated	2 (2%)	6 (6%)
Presumed Eradicated	98 (93%)	79 (82%)
Persisted	-	-
Presumed Persisted	4 (4%)	7 (7%)
Persisted without Acquisition of Resistance	1 (1%)	3 (3%)
Unknown	-	1 (1%)
	Visit 4	**Visit 4**
Eradicated	3 (3%)	6 (6%)
Presumed Eradicated	97 (92%)	79 (82%)
Persisted	-	-
Presumed Persisted	4 (4%)	7 (7%)
Persisted without Acquisition of Resistance	1 (1%)	3 (3%)
Unknown	-	1 (1%)
	PostStudy	**PostStudy**
Eradicated	2 (2%)	8 (8%)
Presumed Eradicated	91 (87%)	68 (71%)
Microbiologic Relapse	-	1 (1%)
Presumed Microbiologic Relapse	2 (2%)	1 (1%)
Unknown	6 (6%)	3 (3%)
Presumed Persisted	4 (4%)	8 (8%)

Microbiologic Eradication Rates for the Pathogens of Interest per Sponsor:

Table 7 shows the microbiologic eradication rate for *Streptococcus pneumoniae*. The overall eradication rate (includes presumed eradicated) for *Streptococcus pneumoniae* at the posttherapy visits was 91% for the 750 mg levofloxacin 5-day regimen and 80% for the 500 mg levofloxacin 10-day comparator regimen. The eradication rate (includes presumed eradicated) for *S. pneumoniae* at the poststudy visit was 90% for the 750 mg group and 85% for the 500 mg group. The persistence rate (includes presumed persisted) at posttherapy visits for the 750 mg and 500 mg q.d. groups was 10% and 15%, respectively. The persistence rate (includes presumed persisted) at poststudy visit for the 750 mg and 500 mg groups was 5% and 10%, respectively. At poststudy, there were no microbiologic relapses for either study group.

Table 7: Microbiologic Eradication Rate for *Streptococcus pneumoniae*

Streptococcus pneumoniae	750 mg q.d. 5-day Regimen n=21	500 mg q.d. 10-day Regimen n=20
	Visit 3	**Visit 3**
Eradicated	-	3 (15%)
Presumed Eradicated	19 (90%)	13 (65%)
Persisted	-	-
Presumed Persisted	1 (5%)	1 (5%)
Persisted without Acquisition of Resistance	1 (5%)	2 (10%)
Unknown	-	1 (5%)
	Visit 4	**Visit 4**
Eradicated	1 (5%)	3 (15%)
Presumed Eradicated	18 (86%)	13 (65%)
Persisted	-	-
Presumed Persisted	1 (5%)	1 (5%)
Persisted without Acquisition of Resistance	1 (5%)	2 (10%)
Unknown	-	1 (5%)
	PostStudy	**PostStudy**
Eradicated	-	3 (15%)
Presumed Eradicated	19 (90%)	14 (70%)
Microbiologic Relapse	-	-
Presumed Microbiologic Relapse	-	-
Unknown	1 (5%)	1 (5%)
Presumed Persisted	1 (5%)	1 (5%)
Persisted without Acquisition of Resistance	0	1 (5%)

Table 8 demonstrates the microbiologic eradication rate for *Haemophilus influenzae*. The overall eradication rate (including presumed eradicated) for *Haemophilus influenzae* at the posttherapy visits was 100% for the 750 mg levofloxacin 5-day regimen and 83% for the 500 mg levofloxacin 10-day regimen. The poststudy eradication rate (including presumed eradicated) was 83% for the 750 mg group and 83% for the 500 mg group. The persistence rate (including presumed persisted) at the posttherapy visit was 0% for the 750 mg group and 16% for the 500 mg group. The persistence rate (including presumed persisted) at the poststudy visit was 0% for the 750 mg group and 8% for the 500 mg group. There were no microbiologic relapses at the poststudy visit for either treatment group.

Table 8: Microbiologic Eradication Rate for *Haemophilus influenzae*

Haemophilus influenzae	750 mg q.d. 5-day Regimen n=12	500 mg q.d. 10-day Regimen n=12
	Visit 3	**Visit 3**
Eradicated	-	-
Presumed Eradicated	12 (100%)	10 (83%)
Persisted	-	-
Presumed Persisted	-	1 (8%)
Persisted without Acquisition of Resistance	-	1 (8%)
Unknown	-	-
	Visit 4	**Visit 4**
Eradicated	-	-
Presumed Eradicated	12 (100%)	10 (83%)
Persisted	-	-
Presumed Persisted	-	1 (8%)
Persisted without Acquisition of Resistance	-	1 (8%)
Unknown	-	-
	PostStudy	**PostStudy**
Eradicated	-	1 (8%)
Presumed Eradicated	10 (83%)	9 (75%)
Microbiologic Relapse	-	-
Presumed Microbiologic Relapse	-	-
Unknown	2 (17%)	1 (8%)
Relapsed	-	-
Presumed Persisted	-	1 (8%)

Table 9 shows the microbiologic eradication rate for *Haemophilus parainfluenzae*. The overall eradication rate (including presumed eradicated) for *Haemophilus parainfluenzae* at the posttherapy visits and poststudy visit was 100% for the 750 mg levofloxacin 5-day regimen and 89% for the 500 mg levofloxacin 10-day regimen. The persistence rate (including presumed persisted) at posttherapy and poststudy visits was 0% for the 750 mg group and 11% for the 500 mg group. There were no microbiologic relapses for either treatment regimen.

Table 9: Microbiologic Eradication Rate for *Haemophilus parainfluenzae*

Haemophilus parainfluenzae	750 mg q.d. 5-day Regimen n=10	500 mg q.d. 10-day Regimen n=9
	Visit 3	**Visit 3**
Eradicated	-	-
Presumed Eradicated	10 (100%)	8 (89%)
Persisted	-	-
Presumed Persisted	-	1 (11%)
Persisted without Acquisition of Resistance	-	-
Unknown	-	-
	Visit 4	**Visit 4**
Eradicated	-	-
Presumed Eradicated	10 (100%)	8 (89%)
Persisted	-	-
Presumed Persisted	-	1 (11%)
Persisted without Acquisition of Resistance	-	-
Unknown	-	-
	PostStudy	**PostStudy**
Eradicated	-	-
Presumed Eradicated	10 (100%)	8 (89%)
Microbiologic Relapse	-	-
Presumed Microbiologic Relapse	-	-
Unknown	-	-
Relapsed	-	-
Presumed Persisted	-	1 (11%)

Table 10 below demonstrates the microbiologic presumed eradication rate for *Chlamydia pneumoniae*. The overall presumed eradication rate for *Chlamydia pneumoniae* at the posttherapy visits was 87% for the 750 mg levofloxacin 5-day regimen and 100% for the 500 mg levofloxacin 10-day regimen. The presumed eradication rate at the poststudy visit was 80% for the 750 mg group and 83% for the 500 mg group. The presumed persistence rate for the posttherapy and poststudy visits was 13% for the 750 mg group and 0% for the 500 mg group. There were no presumed microbiologic relapses at the poststudy visits for either study group.

Table 10: Microbiologic Presumed Eradication Rate for *Chlamydia pneumoniae*

Chlamydia pneumoniae	750 mg q.d. 5-day Regimen n=15	500 mg q.d. 10-day Regimen n=6
	Visit 3	**Visit 3**
Presumed Eradicated	13 (87%)	6 (100%)
Presumed Persisted	2 (13%)	-
Unknown	-	-
	Visit 4	**Visit 4**
Presumed Eradicated	13 (87%)	6 (100%)
Presumed Persisted	2 (13%)	-
Unknown	-	-
	PostStudy	**PostStudy**
Presumed Eradicated	12 (80%)	5 (83%)
Presumed Microbiologic Relapse	-	-
Unknown	1 (7%)	1 (17%)
Presumed Persisted	2 (13%)	-

Table 11 demonstrates the overall presumed eradication rate at the posttherapy visits for *Mycoplasma pneumoniae* which was 96% for the 750 mg levofloxacin 5-day regimen and 92% for the 500 mg levofloxacin 10-day regimen. The presumed eradication rate at the poststudy visit was 85% for the 750 mg group and 88% for the 500 mg group. The presumed persistence rate at the posttherapy and poststudy visits was 4% and 8% for the 750 mg and 500 mg groups, respectively. The presumed microbiologic relapse rate was 7% and 1% for the 750 mg and 500 mg groups, respectively.

Table 11: Microbiologic Presumed Eradication Rate for *Mycoplasma pneumoniae*

Mycoplasma pneumoniae	750 mg q.d. 5-day Regimen n=27	500 mg q.d. 10-day Regimen n=26
	Visit 3	**Visit 3**
Presumed Eradicated	26 (96%)	24 (92%)
Presumed Persisted	1 (4%)	2 (8%)
Unknown	-	-
	Visit 4	**Visit 4**
Presumed Eradicated	26 (96%)	24 (92%)
Presumed Persisted	1 (4%)	2 (8%)
Unknown	-	-
	PostStudy	**PostStudy**
Presumed Eradicated	23 (85%)	23 (88%)
Presumed Microbiologic Relapse	2 (7%)	1 (4%)
Unknown	1 (4%)	-
Presumed Persisted	1 (4%)	2 (8%)

Table 12: Microbiologic Presumed Eradication Rate for

	750 mg q.d. 5-day Regimen	500 mg q.d. 10-day Regimen

Atypical Pathogen Distribution Based on Case Definitions in CAPSS-150 Protocol:

Table 13 below summarizes the atypical pathogen distribution per the case definitions in the CAPSS-150 Protocol for the clinically and microbiologically evaluable populations.

Table 13: Atypical Pathogen Distribution Based on Case Definitions in CAPSS-150 Study

Pathogen	**750 mg, 5-day**	**500 mg, 10-day**	**Total**
Chlamydia pneumoniae IgG (Fourfold increase/decrease in titer at Visit 3 and 5)	12	6	18
Chlamydia pneumoniae IgM (Fourfold increase/decrease in titer at Visit 3 and 5)	9	2	11
Total minus repeats	**15**	**6**	**21**
Mycoplasma pneumoniae IgG	21	20	41
Single > 1:128 Titer	7	7	14
Fourfold increase/decrease at visit 3 and 5	14	13	27
Mycoplasma pneumoniae IgM	11	7	18
Single >1:16 titer	8	2	10
fourfold increase/decrease at visit 3 and 5	3	5	8
Total minus repeats	**27**	**26**	**53**

SuperInfections:

A superinfection was defined as an organism identified or obtained after admission and up to or including the test-of-cure visit which, based on Gram stain, culture results, and susceptibility, was involved in any infectious process and which required specific new antimicrobial therapy. In the ITT population, four subjects in the levofloxacin 750 mg group and six subjects in the levofloxacin 500 mg group developed superinfections. The infecting pathogens were *S. pneumoniae*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, *Candida albicans*, and *Pseudomonas maltophila.* These identified superinfections were not included by the Sponsor in the clinically or microbiologically evaluable populations.

New Infectors:

New infectors were defined as organisms other than those identified at admission, isolated from the respiratory tract or blood after the test-of-cure visit, associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of acute pneumonia, and requiring antimicrobial therapy. Two subjects, both in the levofloxacin 500 mg group, had new infectors. One had *Moraxella catarrhalis* and *S. pneumoniae* isolated from the sputum, and the other had *H. influenzae* isolated from the sputum.

FDA Conclusions from CAPSS-150 Study:

The microbiologic eradication rates per pathogen seem to be higher for the 750 mg q.d. oral levofloxacin 5-day regimen treatment group than for the 500 mg q.d. oral levofloxacin 10-day regimen group. The microbiologic relapse rates were comparable at poststudy for the 750 mg and 500 mg group with a rate of 2%. The overall pathogen persistence rates were higher for the 500 mg 10-day regimen versus the 750 mg 5-day regimen.

Regarding the pathogens of interest isolated from respiratory cultures (typical pathogens), the microbiologic eradication rates at posttherapy visits were about 10% higher for the 750 mg group for *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Streptococcus pneumoniae*. However, at the poststudy visits, the microbiologic eradication rates for the 750 mg and 500 mg treatment groups were comparable for the typical pathogens. Therefore, the 750 mg dose seems to have more of an effect against the typical pathogens within the first 12-21 days of the study. By day 17-24 of the study, the effectiveness of the 500 mg 10-day and 750 mg 5-day regimens are almost equivalent. For both *H. influenzae* and *H. parainfluenzae*, there was no persistence noted for the 750 mg group. The persistence rate for both *H. influenzae* and *H. parainfluenzae* for the 500 mg treatment group was 8% and 11%, respectively. For *S. pneumoniae*, the persistence rates for the 500 mg group were also higher than those of the 750 mg treatment group. There were no microbiologic relapses noted for either treatment group for these typical respiratory pathogens.

Regarding the pathogens of interest identified by serology, the microbiologic eradication rates were 100% for [redacted] for both treatment groups. For *Chlamydia pneumoniae*, the 500 mg 10-day regimen seemed more effective with a presumed eradication rate of 100% versus 87% for the 750 mg treatment group. However, at poststudy, the 500 mg and 750 mg treatment groups had very similar presumed eradication rates for *Chlamydia pneumoniae*. The persistence rate was much higher for the 750 mg treatment versus the 500 mg treatment regimen which had no persistence throughout posttherapy/poststudy. For *Mycoplasma pneumoniae*, the presumed eradication rates for the 750 mg and 500 mg groups were very similar throughout posttherapy and poststudy. The presumed persistence rates for the 500 mg groups were higher than the 750 group. For *C. pneumoniae* an [redacted], no microbiologic relapses were noted for either treatment group. For *Mycoplasma pneumoniae*, the microbiologic relapse rate for the 750 group was moderately higher than the relapse rate for the 500 mg group.

Study Design of CAPSS-171:

A supportive, multicenter, open-label, non-comparative, Phase 3B study to evaluate the safety and efficacy of levofloxacin 750 mg once daily for five days in the treatment of mild to severe community-acquired pneumonia (CAP) in adults. Up to 200 subjects with a diagnosis of CAP were to be enrolled in the study. The key inclusion/exclusion criteria were similar to those of the pivotal study. The CAPSS-171 study provided an opportunity for a subject who did not meet certain inclusion criteria of the CAPSS-150 study to be enrolled in a 750 mg q.d., five-day treatment program. The efficacy endpoints included clinical and microbiological outcomes. Microbiologic outcomes were to be determined for subjects who had a pathogen identified at admission. Microbiologic response was to be assessed at the Posttherapy Visit (Study Day 12-16, 7 to 14 days after completion of therapy) and at the Poststudy Visit (Study day 26-33) for subjects who were clinically cured or improved at posttherapy. Subjects who had a negative culture posttherapy or poststudy were to be classified as having their pathogens eradicated; the pathogens of subjects with no samples to culture were to be classified as presumed eradicated. For pathogens identified by serology or urine antigen testing, the microbiologic response at posttherapy or poststudy was to be based on the clinical response at the corresponding visit. The criteria for assigning clinical and microbiological response rates were the same as those used in the pivotal study.

Microbiology Results

In Vitro Susceptibility

Table 14 presents a summary of the *in vitro* susceptibility of pathogens isolated at admission from respiratory or blood cultures of ITT subjects. A total of 52 admission pathogens were isolated. Forty-seven pathogens were tested for susceptibility to the study drug. Forty-four of the 47 pathogens with known susceptibility to levofloxacin were either susceptible (91.5%; 43/47) or had intermediate susceptibility (2.1%; 1/47) to the drug. Three (6.4%) isolates were resistant to levofloxacin.

Table 14: In Vitro Susceptibility of Respiratory and Blood Pathogens Identified at Admission: Intent-to-Treat Population (Study CAPSS-171)

	Levofloxacin 750 mg q.d.5-day Regimen	
Susceptibility of Pathogen[b]	n	(%)[a]
Susceptible	43	(91.5)
Intermediate	1	(2.1)
Resistant	3	(6.4)
Unknown Susceptibility	5	
Total No. Pathogens	52	

[a] Percentages were based on the total numbers of pathogens with known susceptibilities to levofloxacin.
[b] Pathogens were identified in 39 subjects.
**Adapted from Table 20 of CAPSS-171 Study Report*

The following subject numbers were excluded from the atypical pathogen population due to noncompliance with the case definitions as written in the CAPSS-171 Study Report (same as CAPSS-150 study report):

Chlamydia pneumoniae	*Mycoplasma pneumoniae*
16001	9018
	106003

FDA Analysis of Microbiological Efficacy (microbiologically evaluable population)

Microbiologic Eradication Rate by Subject's Infection:

Table 15 demonstrates the overall eradication rate (including presumed eradication) by subject at the posttherapy visit and poststudy visit for the 750 mg levofloxacin 5-day regimen was 80% and 59%, respectively. The persistence rate (including presumed persisted) at posttherapy was 16% and 14% at poststudy. The microbiologic relapse rate (including presumed relapse) was 2%.

Table 15: Microbiologic Eradication Rates (by subject)

	750 mg q.d. 5-day Regimen n=44
	Posttherapy
Eradicated/Presumed Eradicated	35 (80%)
Persisted/Presumed Persisted	7 (16%)
Unknown	2 (5%)
	PostStudy
Eradicated/Presumed Eradicated	30 (59%)
Relapsed/Presumed Relapsed	1 (2%)
Unknown	7 (16%)
Persisted/Presumed Persisted	6 (14%)

Microbiologic Eradication Rate by Pathogen:

Table 16 demonstrates the overall microbiologic eradication rate by pathogen. The overall eradication rate (including presumed eradication) per pathogen at the posttherapy visit and poststudy visit for the 750 mg levofloxacin 5-day regimen was 84% and 73%, respectively. The persistence rate (including presumed persisted) at posttherapy and poststudy was 13% and 11% respectively. The microbiologic relapse rate (including presumed relapse) was 2%.

Table 16: Microbiologic Eradication Rate (by pathogen)

	750 mg q.d. 5-day Regimen n=44
	Posttherapy
Eradicated	7 (16%)
Presumed Eradicated	30 (68%)
Persisted with Acquisition of Resistance	1 (2%)
Presumed Persisted	5 (11%)
Unknown	1 (2%)
	PostStudy
Eradicated	8 (18%)
Presumed Eradicated	24 (55%)
Presumed Relapsed	1 (2%)
Unknown	6 (14%)
Presumed Persisted	5 (11%)

Microbiologic Eradication Rate for the pathogens of interest:

Table 17 demonstrates the microbiologic eradication rate for *Streptococcus pneumoniae*. The overall eradication rate (including presumed eradicated) for *Streptococcus pneumoniae* at posttherapy and poststudy for the 750 mg levofloxacin 5-day regimen was 77% and 66%, respectively. The persistence rate (including presumed persisted) at posttherapy and poststudy was 11%. There were no microbiologic relapses at poststudy.

Table 17: Microbiologic Eradication Rate for *Streptococcus pneumoniae*

Streptococcus pneumoniae	750 mg q.d. 5-day Regimen n=9
	Posttherapy
Eradicated	3 (33%)
Presumed Eradicated	4 (44%)
Persisted with Acquisition of Resistance	-
Presumed Persisted	1 (11%)
Unknown	1 (11%)
-	-
	PostStudy
Eradicated	3 (33%)
Presumed Eradicated	3 (33%)
Presumed Relapsed	-
Unknown	1 (11%)
Presumed Persisted	1 (11%)

Table 18 shows the microbiologic eradication rate for *Haemophilus influenzae*. The overall eradication rate (including presumed eradicated) for *Haemophilus influenzae* at posttherapy and poststudy for the 750 mg levofloxacin 5-day regimen was 80% and 60%, respectively. The persistence rate (including presumed persisted) at posttherapy and poststudy was 20%. There were no microbiologic relapses at poststudy.

Table 18: Microbiologic Eradication Rate for *Haemophilus influenzae*

Haemophilus influenzae	750 mg q.d. 5-day Regimen n=5
	Posttherapy
Eradicated	-
Persisted with Acquisition of Resistance	-
Presumed Eradicated	4 (80%)
Presumed Persisted	1 (20%)
Unknown	-
	PostStudy
Eradicated	-
Presumed Eradicated	3 (60%)
Presumed Relapsed	-
Unknown	1 (20%)
Presumed Persisted	1 (20%)

Table 19 shows the microbiologic eradication for *Haemophilus parainfluenzae*. The overall eradication rate (including presumed eradicated) for *Haemophilus parainfluenzae* at the posttherapy and poststudy visit for the 750 mg levofloxacin 5-day regimen was 100% and 85%, respectively. There was no persistence or microbiologic relapse at postherapy or poststudy.

Table 19: Microbiologic Eradication Rate for *Haemophilus parainfluenzae*

Haemophilus parainfluenzae	750 mg q.d. 5-day Regimen n=7
	Posttherapy
Eradicated	1 (14%)
Persisted with Acquisition of Resistance	-
Presumed Eradicated	6 (86%)
Presumed Persisted	-
Unknown	-
	PostStudy
Eradicated	1 (14%)
Presumed Eradicated	5 (71%)
Presumed Relapsed	-
Unknown	1 (14%)

Table 20 shows the microbiologic presumed eradication rate for *Chlamydia pneumoniae*. The overall presumed eradication rate for *Chlamydia pneumoniae* at posttherapy and poststudy for the 750 mg levofloxacin 5-day regimen was 75%. The presumed persistence rate at posttherapy and poststudy was 25%. There were no microbiologic relapses noted.

Table 20: Microbiologic Presumed Eradication Rate for *Chlamydia pneumoniae*

Chlamydia pneumoniae	750 mg q.d. 5-day Regimen n=4
	Posttherapy
Presumed Eradicated	3 (75%)
Presumed Persisted	1 (25%)
Unknown	-
	PostStudy
Presumed Eradicated	3 (75%)
Presumed Relapsed	-
Unknown	-
Presumed Persisted	1 (25%)

Table 21: Microbiologic Presumed Eradication Rate for

Table 22 shows the microbiologic presumed eradication rate for *Mycoplasma pneumoniae*. The overall presumed eradication rate for *Mycoplasma pneumoniae* at posttherapy and poststudy for the 750 mg levofloxacin 5-day regimen was 90% and 80%, respectively. The persistence rate at posttherapy and poststudy was 10% and there were no microbiologic relapses noted at poststudy.

Table 22: Microbiologic Presumed Eradication Rate for *Mycoplasma pneumoniae*

Mycoplasma pneumoniae	750 mg q.d. 5-day Regimen n=10
	Posttherapy
Presumed Eradicated	9 (90%)
Presumed Persisted	1 (10%)
Unknown	-
	PostStudy
Presumed Eradicated	8 (80%)
Presumed Relapsed	-
Unknown	1 (10%)
Presumed Persisted	1 (10%)

Atypical Pathogen Distribution Based on Case Definitions in CAPSS-171 Protocol:

Table 23 below summarizes the atypical pathogen distribution per the case definitions in the CAPSS-171 Protocol for the clinically and microbiologically evaluable populations.

Table 23: Atypical Pathogen Distribution Based on Case Definitions in CAPSS-171

Pathogen	750 mg, 5-day	Total
Chlamydia pneumoniae IgG (Fourfold increase/decrease in titer at Visit 3 and 5)	4	4
Chlamydia pneumoniae IgM (Fourfold increase/decrease in titer at Visit 3 and 5)	0	0
Total minus repeats	4	4
Mycoplasma pneumoniae IgG *Single > 1:128 Titer* *Fourfold increase/decrease at visit 3 and 5*	3 5	8
Mycoplasma pneumoniae IgM *Single >1:16 titer* *fourfold increase/decrease at visit 3 and 5*	4 1	5
Total minus repeats	**10**	**10**

Conclusion:
The CAPSS-171 study is a supportive study to the pivotal CAPSS-150 study so the numbers of pathogens are much lower which causes the eradication rates to seem much lower also. The levofloxacin 750 mg q.d. 5-day regimen was effective at eradicating the primary pathogens of interest per the sponsor with no microbiologic relapses recorded at poststudy.

Sponsor's Proposed Label:

The sponsor has not proposed any changes in the Microbiology section of the label. The specific organisms requested are *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Chlamydia pneumoniae* 1, and *Mycoplasma pneumoniae.* These organisms are already in the clinical efficacy list (list #1) in the microbiology sub-section of the label, so the microbiology section of the label will require no changes.

RECOMMENDATIONS:
From the microbiology standpoint, this supplemental application for the addition of 750 mg q.d. oral 5-day regimen to the label for the treatment of community-acquired pneumonia is acceptable.

_____
Susan Peacock
Microbiology Reviewer, HFD-590

CONCURRENCES:
HFD-590/Deputy Director_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA # 20-634/S-028; NDA 20-635/S-027
HFD-590/Division File
HFD-590/Micro/SPeacock
HFD-590/MO/LSacks
HFD-590/Pharm/SHundley
HFD-590/Chem/Holbert
HFD-590/RPM/SPeacock

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Peter Dionne
9/24/03 03:03:50 PM
MICROBIOLOGIST

Shukal Bala
9/24/03 03:16:52 PM
MICROBIOLOGIST

Kenneth Hastings
10/6/03 11:26:12 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634 / S-028
20-635 / S-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION

LEVAQUIN® (levofloxacin) Tablets and Injection
Supplemental New Drug Application
Short Course Treatment of Community Acquired Pneumonia

Active Ingredient:	Levofloxacin
Strength:	250 mg, 500 mg, 750 mg
Trade Name:	LEVAQUIN®
Dosage Form:	Tablets/Injection
Route of Administration:	Oral/I.V.
U.S. Patent Number:	5,053,407
Expiration Date:	December 20, 2010 (Extended)
Type of Patent:	Drug Substance/Method of Use
Name of Patent Owner:	Daiichi Seiyaku Co., Ltd. Tokyo, Japan
Agent of Patent Owner:	Philip S. Johnson One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003

The undersigned declares that Patent No. 5,053,407 covers the formulation, composition, and/or method of use of LEVAQUIN® (Levofloxacin) tablets and injection. This product is currently approved under section 505 of the Federal Food Drug and Cosmetic Act.

Date: November 5, 2002

Joseph S. Kentoffio
Attorney for Applicant
Registered Patent Attorney
Registration No. 33,189

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Date: November 5, 2002

Joseph S. Kentoffio
Attorney for Applicant
Registered Patent Attorney
Registration No. 33,189

EXCLUSIVITY SUMMARY for NDA # 20-634, 20-635 SUPPL # S-028,S-027

Trade Name LEVAQUIN® Generic Name levofloxacin

Applicant Name Johnson & Johnson Pharmaceutical Research and Development HFD-590

Approval Date October 23, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE2

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity? YES /___/ NO /_X__/

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   e) Has pediatric exclusivity been granted for this Active Moiety?

      YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of

administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-634 levofloxacin Tablets

NDA # 20-635 levofloxacin Injection

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-

approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/ **N/A**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently

would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CAPSS-150

Investigation #2, Study # CAPSS-171

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

   If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

   NDA # _____ Study #
   NDA # _____ Study #
   NDA # _____ Study #

   (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

   If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

   NDA # _____ Study #

   NDA # _____ Study #

   NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # CAPSS-150

Investigation #_, Study # CAPSS-171

Investigation #_, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

!

IND # 36,627
38,638 YES /_X__/ ! NO /___/ Explain:
!

Investigation #2 !

!

IND # 36,627
38,638 YES /_ X__/ ! NO /___/ Explain:
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____
!

_____ ! _____
!

_____ ! _____
!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

Susan Peacock, M.S.
Signature of Preparer Date
Title: Regulatory Project Manager

Renata Albrecht, M.D.
Signature of Division Director Date

cc:
Archival NDA
HFD-590 /Division File
HFD- 590 /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Renata Albrecht

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 20-634, 20-635 Supplement Type (e.g. SE5): SE2 Supplement Number: 028, 027
Stamp Date: December 23, 2003 Action Date: October 23, 2003 HFD 590

Trade and generic names/dosage form: LEVAQUIN® (levofloxacin) Tablets
LEVAQUIN® (levofloxacin) Injection
LEVAQUIN® (levofloxacin in 5% dextrose) Injection

Applicant: Johnson & Johnson Pharmaceutical Research and Development Therapeutic Class: 4030100

Indication(s) previously approved: acute maxillary sinusitis, acute bacterial exacerbation of chronis bronchitis, community-acquired pneumonia, nosocomial pneumonia, complicated skin and skin structure infections, uncomplicated skin and skin structure infections, complicated urinary tract infections, acute pyelonephritis, uncomplicated urinary tract infections, prostatitis.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Community-Acquired Pneumonia, dosing regimen change to 750 mg, once daily for 5 days.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: X Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.__0__	yr.____	Tanner Stage____
Max____	kg____	mo.__6__	yr.____	Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population

- ☐ Disease/condition does not exist in children
- X Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:
{See appended electronic signature page}
Susan Peacock
Regulatory Project Manager

cc: NDA 20-634/S-028, NDA 20-635/S-027
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Susan Peacock
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PEDIATRIC USE Section or Certification Statement

In compliance with 21 CFR 314.55(b), Johnson & Johnson Pharmaceutical Research & Development, L.L.C., (JJPRD) is submitting this statement to NDAs 20-634 and 20-635 for LEVAQUIN® Tablets and Injection respectively. LEVAQUIN® is a synthetic broad spectrum antibacterial agent for oral and intravenous use.

As the indication of short course treatment of community-acquired pneumonia requires a 750 mg dose, JJPRD hereby requests a deferral of pediatric studies for this indication. The deferral is requested until JJPRD has conducted appropriate clinical studies at the standard LEVAQUIN® dose (500 mg equivalent) in pediatrics.

This Supplemental New Drug Application provides efficacy and safety data for short course treatment in patients with Community-Acquired Pneumonia.

Robyn S. Keown

Robyn S. Keown, Manager
Regulatory Affairs

November 22, 2002
Date

TELECON MINUTES

DATE:	October 17, 2003
TIME:	1:30 – 2:00 P.M.
LOCATION:	N466, 9201 Corporate Blvd.
NDA#	NDA 20-634/S-028 and NDA 20-635/S-027
DRUG:	Levaquin®(levofloxacin)
SPONSOR/APPLICANT:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
CONTACT NAME:	Robyn Keown
FAX NUMBER:	(908) 231-0056
PHONE NUMBER:	(908) 704-5317
PROJECT MANAGER:	Susan Peacock, MS
DIVISION OF:	Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590
FORMAT:	Teleconference

FDA PARTICIPANTS, DIVISIONS, AND TITLES:

Rigoberto Roca, M.D., Medical Team Leader, DSPIDP
Leonard Sacks, M.D., Medical Team Leader, DSPIDP
Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader, DSPIDP
Victoria Moncada, M.D., Medical Reviewer, DSPIDP
Susan Peacock, M.S., Regulatory Project Manager, DSPIDP

INDUSTRY PARTICIPANTS AND TITLES:

Alan Tennenberg, MD, OMP-Clinical Research
Robyn Keown, J&JPRD-Regulatory Affairs
Jerry Klimek, J&JPRD-Regulatory Affairs
Jane Rosenblum, MS - Associate Director, Clinical Research, Ortho-McNeil Pharmaceuticals
Mohammed Khashab, OMP-Clinical Research

BACKGROUND:

In a previous labeling telecon, October 10, 2003, the Division informed J&JPRD that the failure rate in the uncontrolled study was higher in the mild to moderate renally-impaired patients than in non-renally impaired patients. J&JPRD said that they also had noted this finding and were unable to explain it, even though they had assessed the data with several types of analyses. The Division's concluding statements at the end of that telecon were that perhaps the study had yielded all that it could, and J&JPRD was asked to think about how to address this finding (not in the label; presumably in a study of some type).

DISCUSSION POINTS:

The Division had a telecon with J&JPRD to follow-up on J&J's plan to address the finding in the CAPSS-171 uncontrolled study. J&JPRD made a verbal presentation of their analyses on the success rates based on renal function (see Attachment 1). Basically, the conclusion was that the success rates were comparable among the following groups of renal clearance:

>80 ml/min 76.3% (n=38)
50-80 ml/min 76.7% (n=30)
20-50 ml/min 79.3% (n=29)

The Division's primary medical reviewer for this project noted that his numbers did not coincide with the numbers being quoted by J&JPRD, presumably because his numbers reflected patients who had dosing adjustments for renal dysfunction. A possible explanation is that it is not the renal impairment that necessarily resulted in the lower efficacy rate observed, but the dose adjustment that was made due to the renal impairment.

During the discussion, J&JPRD confirmed that the dosing recommendations for the 750-mg dose were based on computer simulations, and no representative from J&JPRD that was participating on the telecon had been present when the recommendation of 750 mg q 48 hr for the patients in the 20-50 ml/min stratum was decided upon. J&JPRD acknowledged that a PK study to confirm the dosing recommendation was not unreasonable, unfortunately, there were no representatives from their PK group on the telecon. J&JPRD agreed to take this recommendation back to their PK group and senior management.

The Division also suggested the possible utility of a PK study in renally-impaired patients with CAP (Community-Acquired Pneumonia) based on an expressed interest in the data by the Division Director. J&JPRD intends to bring in additional supplements for their other indications using the 750-mg dose. Therefore, J&JPRD asked if they did a study in renally impaired patients with CAP, could the conclusions be extrapolated to their other indications (specifically mentioned were sinusitis, AECB, and nosocomial pneumonia), or will studies in renally-impaired patients with those infections be necessary. The Division agreed to discuss this question with the Division Director.

ACTION ITEMS:

1. A follow-up telecon will occur on October 21, 2003 to discuss the following:

    a. J&JPRD will provide an answer as to whether a PK study to confirm the dose adjustments in renal failure will be done.

b. The Division will provide an answer as to whether J&JPRD, if they conduct a study in renally-impaired patients with CAP, can extrapolate the conclusions of the study to other indications (ex. Sinusitis, AECB, nosocomial pneumonia).

Susan Peacock, Regulatory Project Manager
Minutes Preparer

Rigoberto Roca, M.D.
Medical Team Leader

Attachment 1 from Sponsor:

P-Value	Creatinine Clearance Group	Intent-To-Treat					
		CAPSS-150			CAPSS-171		
		Total	Success	Failure	Total	Success	Failure
0.070	>80	161	142 (88.2)	19 (11.8)	38	29 (76.3)	9 (23.7)
0.148	50-80	83	73 (88.0)	10 (12.0)	30	23 (76.7)	7 (23.3)
0.639	20-50	7	5 (71.4)	2 (28.6)	29	23 (79.3)	6 (20.7)

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/s/

Rigoberto Roca

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634/S-028
NDA 20-635/S-027

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Robyn S. Keown
Manager, Regulatory Affairs
920 Route 202 South, PO Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Keown:

Please refer to your submissions dated April 24, 2003, requesting a waiver for a 4-month safety update report [as required under 21 CFR 314.50(d)(5)(vi)(b)] for Levaquin® (levofloxacin tablets and injection).

We have reviewed the submission and agree that a waiver is justified for Levaquin® (levofloxacin tablets and injection) for short course treatment of community-acquired pneumonia.

Accordingly, a waiver for a 4-month safety update report for your supplemental applications is granted under 21 CFR 314.90 at this time.

If you have questions, please call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Division Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING ISSUES IDENTIFIED

NDA 20-634/S-028
NDA 20-635/S-027

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Robyn Keown, Manager, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Keown:

Please refer to your supplemental new drug applications dated December 20, 2002, received December 23, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVAQUIN® (levofloxacin) Tablets and Injection, 750 mg.

These supplemental new drug applications provide for:

- A change in the regimen for Community Acquired Pneumonia (CAP). The approved regimen is once daily for 7 to 14 days; the proposed regimen is once daily for 5 days.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on February 21, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

- Case Report Forms for CAPSS-150 study: Please provide all of the case report forms (CRFs) for the CAPSS-150 study electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). Alternatively, you may submit the archival copy of the CRFs in paper.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
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