CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

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

Trade Name: **Levaquin**

Generic Name: **levofloxacin**

Sponsor: **Johnson & Johnson PRD**

Approval Date: **May 23, 2003**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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 dated July 26, 2002, received July 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levaquin (levofloxacin) Tablets (NDA 20-634/S-027); Levaquin (levofloxacin) Injection and Levaquin (levofloxacin in 5% dextrose injection) Injection (NDA 20-635/S-026).

We acknowledge receipt of your submissions dated:

July 26, 2002	December 13, 2002	May 20, 2003
August 26, 2002	March 14, 2003	May 22, 2003 (2)
November 26, 2002 (2)	April 10, 2003	

These supplemental new drug applications provide for the use of Levaquin Tablets and Injection for the treatment of chronic bacterial prostatitis.

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. 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 May 22, 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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-634/S-027, **NDA 20-635/S-026." Approval of these submissions by** the FDA is not required before the labeling is used.

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, we encourage you to submit a pediatric plan that describes development of your products in the pediatric population where they 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 decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of these drug products 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.

Please submit three copies of the introductory promotional materials that you propose to use for this new indication 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 inserts 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, HF-2
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
5/23/03 02:02:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

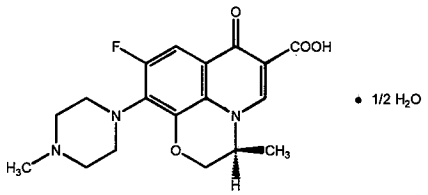
LABELING

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 $C_{18}H_{20}FN_3O_4 \bullet \frac{1}{2} H_2O$ 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): hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.

500 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose, 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): hydroxypropyl methylcellulose, 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

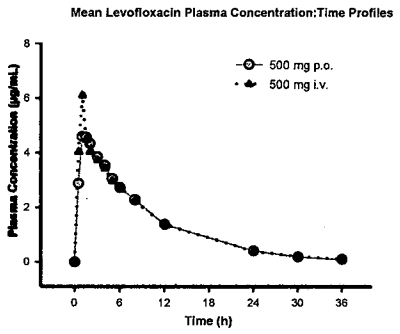
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete 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.

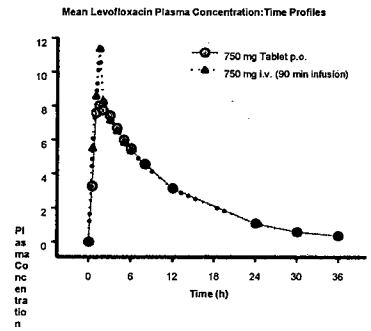
Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral /or i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple 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' differe**nces 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 nonwhite. 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 (µg•h/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	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 (methicillin-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.

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%~~ 6.3%. Among patients receiving levofloxacin therapy, ~~4.1%~~ 4.0% 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 1.3%, diarrhea 1.0%, vaginitis ~~0.7%~~ 0.8% insomnia 0.4%, abdominal pain ~~0.4%~~ 0.5%, flatulence 0.3%, pruritus 0.3%, dizziness 0.3%, dyspepsia 0.3%, rash 0.3%, genital 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%, moniliasis 0.1%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%, maculopapular rash 0.1%.

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

nausea 7.0%, headache 6.1%, diarrhea 5.7%, insomnia ~~4.5%~~ 4.3%, ~~injection site reaction 3.5%,~~ constipation 3.3%.

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

dizziness ~~2.6%~~ 2.5%, abdominal pain ~~2.5%~~ 2.6% dyspepsia 2.3%, vomiting ~~2.4%~~ 2.3%, vaginitis 1.8%, ~~injection site pain 1.7%,~~ flatulence 1.4%, pain 1.4%, pruritus 1.3%, sinusitis 1.3%, chest pain ~~1.2%~~ 1.1%, fatigue 1.3%, rash 1.4%, back pain 1.1%, ~~injection site inflammation 1.1%,~~ rhinitis ~~1.0%~~ 1.1%, ~~taste perversion 1.0%.~~ dyspnea 1.1%, pharyngitis 1.0%.

In clinical trials, the following events, of potential medical importance, occurred at a rate of 0.1% to 1.0%, regardless of drug relationship:

~~Autonomic Nervous System Disorders:~~	~~Postural hypotension~~
Body as a Whole – General Disorders:	Asthenia, fever, malaise, rigors, substernal chest pain, syncope, enlarged abdomen, allergic reaction, ~~headache,~~ hot flashes, edema, influenza-like symptoms, leg pain, multiple organ failure, condition aggravated, peripheral edema
Cardiovascular Disorders, General:	Cardiac failure, circulatory failure, hypertension, hypotension, postural hypotension

Central and Peripheral Nervous System Disorders:	Abnormal coordination, coma, convulsions (seizures), hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo, encephalopathy, abnormal gait, leg cramps, intracranial hypertension, ataxia, migraine
Gastro-Intestinal System Disorders:	Dry mouth, dysphagia, gastroenteritis, G.I. hemorrhage, pancreatitis, pseudomembranous colitis, tongue edema, gastritis, gastroesophageal reflux, melena, esophagitis, stomatitis, intestinal obstruction
Hearing and Vestibular Disorders:	Earache, tinnitus
Heart Rate and Rhythm Disorders:	Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, palpitation, supraventricular tachycardia, ventricular tachycardia, tachycardia, heart block, ventricular fibrillation
Liver and Biliary System Disorders:	~~Elevated bilirubin,~~ Abnormal hepatic function, cholelithiasis, jaundice, hepatic failure, hepatic coma, bilirubinemia
Metabolic and Nutritional Disorders:	Hypomagnesemia, thirst, aggravated diabetes mellitus, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hypokalemia, gout, hypernatremia, hypophosphatemia, increased LDH, weight decrease, fluid overload, electrolyte abnormality
Musculo-Skeletal System Disorders:	Arthralgia, arthritis, arthrosis, pathological fracture, myalgia, osteomyelitis, synovitis, tendonitis, muscle weakness, rhabdomyolysis, skeletal pain
Myo, Endo, Pericardial and Valve Disorders:	Angina pectoris, myocardial infarction, coronary thrombosis
Neoplasms:	Carcinoma
Other Special Senses Disorders:	Parosmia, taste perversion
Platelet, Bleeding and Clotting Disorders:	Pulmonary embolism, hematoma, epistaxis, purpura, thrombocytopenia, abnormal platelets, embolism (blood clot)
Psychiatric Disorders:	Abnormal dreaming, agitation, anorexia, anxiety, confusion, depression, hallucination, nervousness, paranoia, sleep disorder, somnolence, aggressive reaction, delirium, emotional lability, impaired concentration, impotence, manic reaction, mental deficiency, withdrawal syndrome
Red Blood Cell Disorders:	Anemia
Reproductive Disorders:	Dysmenorrhea, leukorrhea, ejaculation failure
Resistance Mechanism Disorders:	Abscess, herpes simplex, bacterial infection, viral infection, moniliasis, otitis media, sepsis, fungal infection, genital moniliasis
Respiratory System Disorders:	Bronchitis, epistaxis, pharyngitis, ~~rhinitis,~~ upper respiratory tract infection, asthma, coughing, dyspnea, hemoptysis, hypoxia, pleural effusion, respiratory insufficiency, airway obstruction, ARDS, aspiration, bronchospasm, emphysema, pneumonia, pneumothorax, pulmonary collapse, pulmonary edema, respiratory depression, respiratory disorder
Skin and Appendages Disorders:	~~Rash,~~ Dry skin, genital pruritus, increased sweating, skin disorder, skin exfoliation, skin ulceration, urticaria, bullous eruption, erythematous rash, maculopapular rash, alopecia, eczema

Urinary System Disorders:	Urinary tract infection, abnormal renal function, acute renal failure, hematuria, face edema, dysuria, oliguria, urinary incontinence, urinary retention
Vascular (Extracardiac) Disorders:	Cerebrovascular disorder, phlebitis, purpura, thrombophlebitis (deep), flushing, gangrene
Vision Disorders:	Abnormal vision, conjunctivitis, diplopia, eye pain
White Cell and RES Disorders:	Granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal (not otherwise specified), leukopenia

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 (~~2.4%~~ 2.3%)

It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

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
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Nosocomial Pneumonia	750 mg	q24h	7-14 days	750 mg
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Acute Maxillary Sinusitis	500 mg	q24h	10-14 days	500 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 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.

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		
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)

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 (500-1000mg 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 N	Levofloxacin No. (%) of Patients Microbiologic / Clinical Outcomes	Imipenem/Cilastatin N	Imipenem/Cilastatin No. (%) of Patients 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 outcomes may reflect other factors that were not accounted for in the study.

Community-Acquired Bacterial Pneumonia

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, multicenter, 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.

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 750mg 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 (=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 ~~Fifth~~ Sixth Edition. Approved Standard NCCLS Document M7 ~~A5~~ A6, Vol. ~~20~~ 23, No. 2, NCCLS, Wayne, PA, January, ~~2000~~ 2003.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests ~~Seventh~~ Eighth Edition. Approved Standard NCCLS Document M2-~~A7~~ A8, Vol. ~~20~~ 23, No. 1, NCCLS, Wayne, PA, January, ~~2000~~ 2003.

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

Revised May 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-634/S027

LEVAQUIN® (levofloxacin) 500 mg tablets and injection in Chronic Bacterial Prostatitis, 28-day regimen

IDENTIFYING INFORMATION

Applicant Identification

Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602
Phone: (908) 704-5317
Fax: (908) 231-0056

Contact Person

Robyn S.Keown
Manager, Regulatory Affairs

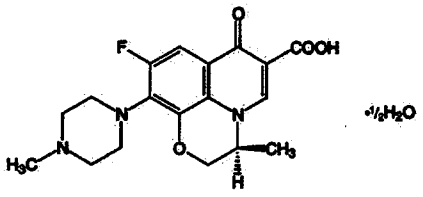
Submission/Review Dates

Date of Submission: July 26, 2002
CDER stamp date: July 26, 2002
Date review begun: August 14, 2002
Date review completed: April 30th, 2003
User fee: # 4358

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	$C_{18}H_{20}FN_3O_4 \cdot ½ H_2O$
Molecular Weight	370.38
Pharmacologic category	fluoroquinolone antimicrobial
Dosage form	Tablets (NDA 20-634) and Solution (NDA 20-635)
Route of Administration	Oral (NDA 20-634) and Parenteral (NDA 20-635)
Strength	500 mg
Related INDs	36,627 and 38,638

Guide to the Clinical Review

Source of Materials

- **The Applicant's study report was used to supply information and details on study** conduct
- Text from outside sources is denoted by a textbox containing the source document
- Medical Officer comments are denoted by a textbox with gray background

List of Abbreviations used in this Review

AE	Adverse event
b.i.d.	bis in die; twice a day
CBP	Chronic bacterial prostatitis
CDER	Center for Drug Evaluation and Research
CFU	Colony forming unit
CI	Confidence interval
CMC	Chemical Manufacturing and Controls
CRF	Case report form
EOS	End-of-study
EOT	End-of-therapy
EPS	Expressed prostatic secretions
FDA	Food and Drug Administration
J&JPRD	Johnson & Johnson Pharmaceutical Research and Development L.L.C.
IDSA	Infectious Disease Society of America
IND	Investigational new drug
ITT	Intent-to-Treat
i.v.	Intravenous
MBE	Microbiologically evaluable
MITT	Modified Intent-to-Treat
MO	Medical Officer
MOR	Medical Officer review
NBE	Nonbacterial evaluable
NDA	New drug application
p.o.	per os
SD	Standard deviation

TMP/SMX	trimethoprim/sulfamethoxazole
TOC	Test-of-Cure
URI	Upper respiratory tract infection
UTI	Urinary tract infection
VB_1	Urethral urine
VB_2	Midstream urine
VB_3	Urine voided after prostatic massage
WBC	White blood cell

Executive Summary

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

From a clinical perspective the recommendation is that levofloxacin be approved for the treatment of chronic bacterial prostatitis (CBP) associated with the following pathogens: *E.coli*, *Enterococcus faecalis* and *Staphylococcus epidermidis*. LEVAQUIN® will provide an advantage in the current armamentarium of antibiotics for CBP in that it will be the only approved once-daily medication. No serious risks were identified in this study. The most common side effects observed with LEVAQUIN® were disorders of the gastrointestinal system.

1.2. Recommendation on Postmarketing Studies and/or Risk Management Steps Where Appropriate.

Review of the data submitted by Applicant in this NDA did not identify any issues that warrant postmarketing studies.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of Clinical Program

In NDA 20-634 S-027 and 20-635 S-026, the Applicant submitted one clinical trial (CAPSS-101) to support the treatment of CBP with LEVAQUIN® 500mg i.v./p.o for 28 days. The population studied was males with chronic bacterial prostatitis; the population was predominantly Caucasian. The enrollment population consisted of 383 patients; 377 patients who received at least one dose of study drug were part of the safety and intent-to-treat population.

Efficacy

CAPSS-101 compared a 28-day course of levofloxacin to ciprofloxacin for the treatment of chronic bacterial prostatitis. LEVAQUIN® has extensive information regarding its use in urinary tract infections, including approval for treatment of complicated UTIs. Therefore, consideration for approval for CBP on the basis of one adequately-controlled, well-conducted study is possible. The applicant met the primary efficacy endpoint of microbiologic eradication in the microbiologically evaluable population at the posttherapy visit (5-18 days after completion of therapy) with 75% (102/136) eradication in the levofloxacin arm and 76.8% (96/125) eradication in the ciprofloxacin arm. The 95% CI was -12.58, 8.98 within the pre-specified delta of 20%. This demonstrates **that levofloxacin's microbiologic response rate is no more than 13% lower** than that of ciprofloxacin. The primary efficacy outcome is consistent with FDA/CDER draft guidance, which requires a microbiologic outcome for the indication of prostatitis. This is the most appropriate outcome in a chronic condition with exacerbations of baseline symptoms that can be challenging to

diagnose. Secondary endpoints at the posttherapy visit corroborate the efficacy of LEVAQUIN® in the treatment of chronic bacterial prostatitis. Secondary endpoints at the poststudy visit (24-45 days after completion of therapy) such as long-term eradication and clinical success were better for ciprofloxacin. Clinical success was 66.7% for the levofloxacin arm compared to 76.9% in the ciprofloxacin arm. This indicates that the long-term success for levofloxacin was lower than that of ciprofloxacin at poststudy (95% CI [-23.40, 2.89]). This difference in outcomes at the poststudy visit will be addressed in labeling. CAPSS-101 was a well-designed multi-center, randomized and blinded study. The study enrolled appropriate and relevant populations and is the basis for the approval of LEVAQUIN® for the treatment of CBP.

2.2. Safety

A patient was included in the safety evaluable population if he received at least one dose of study drug and safety information was available. The safety evaluable population included 197 patients in the levofloxacin treatment group and 180 patients in the ciprofloxacin treatment group. Adverse events were reported for the period of on-therapy to 30 days after last dose of study drug. The mean duration of levofloxacin treatment was 26.6 with a range of 1-44 days. The recommended duration of therapy for this indication is 28 days. Clinically this will likely be the duration of therapy used; though clinicians sometimes prolong duration of therapy to six weeks in the treatment of CBP. The population included in this study is representative of the population that is expected to use this product for this indication.

Significant Adverse Events

One death occurred in the levofloxacin arm of the study [redacted], after the last dose of levofloxacin and assessment by Applicant and Medical Officer did not reveal a relationship of event to drug. Adverse events which led to discontinuation of therapy were found in 11/197 (5.6%) in the levofloxacin arm and 8/180 (4.4%) in the ciprofloxacin arm. In the levofloxacin arm, events which were found in more than one patient were abdominal pain, diarrhea and dyspepsia.

Common Adverse Events

One treatment-emergent adverse event was experienced by 44.2% of levofloxacin patients (87/197) compared to 37.2% of the ciprofloxacin patients (67/180). The most common body system involved was the gastrointestinal system. The most common adverse events were headache, nausea and abdominal pain (6.1%, 5.6%, 5.1% respectively).

Comparison to approved products

In terms of safety, LEVAQUIN® is as safe as CIPRO® which is approved for

CBP. The overall number of adverse events in CAPSS-101 is similar between the two drugs.

Overdosage

Levofloxacin exhibits a low potential for acute toxicity. Animals receiving a single high dose of levofloxacin experienced 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.

No clinically relevant changes in laboratory parameters, no deaths or serious AEs attributable to study-drug were observed in CAPSS-101.

2.3. Dosing, Regimen, and Administration

The dosing regimen proposed for CBP is LEVAQUIN® 500mg p.o. q.d. for 28 days. This is the same dose and frequency for LEVAQUIN®'s other approved indications: acute bacterial exacerbation of chronic bronchitis, community acquired pneumoniae, acute maxillary sinusitis, uncomplicated skin and skin structure infection. The length of therapy for these other indications ranges from 7-14 days. This would be the first indication granted for an extended period of therapy of 28 days. The safety profile of CAPSS-101 was consistent with other Phase 3 studies. A higher dose, 750mg, has been approved for the treatment of complicated skin and skin structure infection in these studies a higher rate of AEs was observed than that observed in CAPSS-101.

2.4. Drug-Drug Interactions

Chelation by divalent cations is less marked than with other quinolones. However, sucralfate, antacids and multivitamins (containing magnesium, aluminum, iron, or zinc) may interfere with gastrointestinal absorption of LEVAQUIN® tablets. Co-administration with non-steroidal anti-inflammatory drugs may increase the risk of central nervous system stimulation and convulsive seizures. The above drug interactions are interactions known and recognized for other quinolones and clinicians should be able to identify them.

2.5. Special Populations

Chronic bacterial prostatitis is only found in adult males. No children or women were included in this trial.

Gender

All patients in this study were male.

Race

The majority of the patients in CAPSS-101 were Caucasian. Twenty-one Black patients were included in the levofloxacin MITT population. No differences in efficacy outcomes at the posttherapy visit were found between Black and Caucasian patients. Too small a number of Asian patients were included to draw any meaningful conclusions. Fewer adverse events were observed among Black patients in CAPPS-101 than in Caucasians (25.0% vs. 49.3%). This trend was also observed in other levofloxacin Phase 3 trials.

Clinical Review

1. Introduction and Background

1.1. Established and Proposed Trade Name of Drug, Drug Class, Applicant's Proposed Indication, Dose, Regimens, Age Groups

LEVAQUIN® (levofloxacin) is a chiral fluorinated carboxyquinolone, the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The applicant, Johnson & Johnson Pharmaceutical Research and Development L.L.C. (J&JPRD) is seeking, on behalf of Ortho-McNeil Pharmaceuticals Inc., the marketing approval for levofloxacin 500mg orally and intravenously once daily for 28 days for the treatment of chronic bacterial prostatitis (CBP) in adults.

1.2. State of Armamentarium for Indication

Three quinolone antibiotics have been approved in the US for the indication of CBP: and ciprofloxacin.

The only currently approved agent for CBP is CIPRO® (ciprofloxacin hydrochloride).

Text from the Physicians' Desk Reference

CIPRO® is indicated for the treatment of...Chronic Bacterial Prostatitis caused by *Escherichia Coli* or *Proteus mirabilis*.

Other antibiotics have been approved for use in prostatitis these include: ANCEF®, KEFLEX®, FLOXIN®, GEOCILLIN® and NOROXIN®, Cefoperazone, Cefotaxime, Cephalotin and Cephradine.

MO Comment: These labels reflect prior language used in the 1992 Points to Consider Document which referred only to bacterial prostatitis and did not differentiate between acute and chronic as is now done.

Text from the Physicians' Desk Reference

ANCEF®
GENITAL INFECTIONS (i.e., prostatitis, epididymitis) due to *Escherichia coli*, *Proteus mirabilis*, Klebsiella species and some strains of Enterococci

KEFLEX® Tablets and Pulvules

Genitourinary tract infections, including acute prostatitis, caused by *E. coli*, *P. mirabilis*, and *K. pneumoniae*

FLOXIN® Tablets and I.V. (ofloxacin)
Prostatitis due to *Escherichia coli*

GEOCILLIN® TABLETS (carbenicillin indanyl sodium)
Geocillin is also indicated in the treatment of prostatitis due to susceptible strains of the following organisms: *Escherichia coli*, Enterococcus (*S. faecalis*),*Proteus mirabilis*,Enterobacter sp

NOROXIN® Tablets (Norfloxacin)
Prostatitis due to *Escherichia coli*.

Text from the USP DI® Drug information for the Health Care Professional-23rd Edition (2003). Cephalosporins mononograph.

Cefazolin, cefoperazone, cefotaxime, cephalexin, and cephradine are indicated in the treatment of genitourinary tract infections, including epididymitis and prostatitis.

MO Comment: There are a variety of products approved for the treatment of CBP which are safe and effective. However, no product currently approved is a once-a-day formulation

1.3. Important Milestones in Product Development

Meetings

On Aug 10, 1999 the Applicant submitted protocol CAPSS-101 for Agency review. The reviewing medical officer, Dr. Leonard Sacks, commented that pain on digital examination was both a requirement for inclusion into the study and was listed under the clinical symptoms. Patients must have prostate tenderness, in addition to at least one symptom to be included in this trial. **"Pain on digital examination is already a requirement and should not be repeated in the list of ancillary symptoms." Pain on digital examination was** removed from the list of ancillary symptoms used to enroll patients.

Protocol was modified per FDA comments and the following exclusion criteria were added: receipt of a quinolone for any reason within the preceding 14 days, receipt of potentially effective therapy within the preceding seven days unless there was documented evidence of an organism resistant to that therapy or of failure to respond to that therapy, requirement for a second systemic antibacterial regimen, requirement for medication that could have affected bladder or prostate function, and known prostatic carcinoma.

Microbiologic response for patient's infection was classified into eradicated, persisted, or unknown. As per our comments communicated to Applicant, the FDA guidance includes superinfection as a category of microbiological response. The Applicant did not include this category. A patient with symptomatic superinfection within the urinary system was to be considered a clinical failure during posttherapy evaluation.

Applicant submitted a protocol amendment on March 16th 2000, in which the definition of chronic prostatitis was amended to one previous clinical diagnosis of prostatitis for a symptomatic episode that lasted at least four weeks or two or more other episodes of any duration during the previous **twelve months. Previously defined as: "previous episodes of symptomatic prostatitis." The Applicant also included as a criterion for evaluability, the** requirement for a study drug exposure between 80% and 120% of the prescribed dose.

Guidelines and Regulatory Guidance

IDSA/FDA[1]

Guidelines state that "it should be assumed that any UTI in a man, especially in those older than 40 years, is associated with bacterial invasion of the **prostate/and or kidney... Because the differentiation in most men between** bacterial prostatitis and bacterial UTI is artificial and inaccurate, this **distinction should be eliminated for the purposes of clinical trials."**
Under the section of trial design, inclusion criteria for studies of UTIs in men are: dysuria, urgency, frequency or suprapubic pain; urinalysis with ≥10 WBCs/mm^3 and ≥10^4 colony-forming units (CFUs) of a uropathogen/ml in midstream urine. The guidelines define acute UTI in patients who are symptom-free for >6 months and as having a chronic UTI those that have had symptomatic infection with the same organism at least once in the 6 months before enrollment. Study design includes an entry visit, a visit 3-5 days after entry, a TOC visit 5-9 days after therapy is completed, with a follow-up visit 4-6 weeks after completion of therapy.

Response rates in men with chronic UTI are expected to be similar to those observed in complicated UTI. Rates for chronic disease would differ from acute disease in that the improved at TOC would be >65% (instead of >75%) and eradication at follow-up would be >40%(instead of >50%).

[1] Rubin RH et al. General Guidelines for the Evaluation of New Anti-Infective Drugs for the Treatment of Urinary Tract Infection. Clinical Infectious Diseases 1992;15(Suppl 1):S216-227.

FDA/CDER Draft Guidance for Industry[2]

This draft guidance for industry was developed by CDER in 1998.

- It states that if effectiveness of the compound has already been established in complicated urinary tract infections, a statiscally adequate and well-controlled multicenter trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product).
- Patients enrolled in studies should meet the following criteria:
  - a soft, tender prostate without nodules consistent with a diagnosis of chronic prostatitis
    and
  - one or more symptoms from the following group: disturbances of urination, including frequency, urgency, dysuria, and/or lower urinary tract obstruction (more commonly seen in patients with chronic disease), hesitancy, decreased stream, urinary retention; perineal or low back pain; fevers; or chills.
- Patients should be both clinically and microbiologically evaluable.
- The assessment for inclusion should include the evaluation of sequential urine cultures as described by Meares and Stamey. This technique includes collection of the following four specimens:
  - Voided bladder 1 (VB1) initial 5-10 ml of urine specimen
  - Voided bladder 2 (VB2) clean-catch midstream urine specimen
  - Expressed prostatic secretions (EPS) secretions expressed from the prostate by digital massage after midstream urine specimen
  - Voided bladder 3 (VB3) First 5-10 ml of urine stream immediately after prostatic massage
- The diagnosis of chronic bacterial prostatitis is confirmed by one of the following criteria:
  - The colony count of a pathogen in VB3 exceeds that in VB1 or VB2 by 10 fold
  - The colony count of a pathogen in EPS exceeds that in VB1 or VB2 by 10 fold
- Studies would include tissue distribution studies that demonstrate the investigative agent diffuses into prostatic secretions and tissues in quantities adequate to achieve and maintain prostatic secretions and tissue levels of antimicrobial compound equal to or above the expected MIC90 of the claimed pathogens for an adequate time period.
- Majority of cases of acute and chronic bacterial prostatitis are caused by *Escherichia coli*, *Enterococcus faecalis*, *Proteus mirabilis* with *Pseudomonas aeruginosa* occasionally. *Staphylococcus aureus* can cause acute bacterial prostatitis in relation to catheters
- Coagulase-negative staphylococci can be considered pathogens, more commonly in chronic bacterial prostatitis of a recurrent nature. The

[2] http://www.fda.gov/cder/guidance/index.htm

isolation of coagulase-negative staphylococci will generally not be considered evidence of an etiologic pathogen. These are generally considered to represent contamination.

Pertinent Advisory Committee meetings

The 64th Anti-Infective Drug Advisory Committee Meeting was held on July 30th, 1998. At this meeting the following concepts were discussed:

- The need to make a distinction between acute and chronic prostatitis
- Diagnosis based on tender exam and the presence of symptoms and on positive microbiology cultures
- Defining eradication more precisely and using 10^3 as the cutoff for a positive culture
- The renaming of clinical relapse to recurrence as is done in UTI for consistency
- Using complete resolution of symptoms as clinical cure and eliminating the category of clinical improvement until a validated scoring system is accepted

Prior FDA reviews

Clinical and Microbiologic Outcomes of Other Quinolone NDA's for CBP

Pivotal Study°	Clinical Cure	Success♦	Eradication EOT	Eradication EOS	Pathogen n/N (%)
[redacted]					
Temofloxacin (no comparator)	57/81 (70%)	74/81 (91%)	73/78 (94%)	97%	*E.coli* 35/36 (97) *E.faecalis* 14/16 (88) *S.epidermis* 9/9
[redacted]					
Norfloxacin*	40/53 (75%)	52/53 (98%)	51/53 (96%)	80%	*E.coli* 29/33 (88)
US Study	16/18 (89%)	17/18 (94%)	16/18 (89%)		*S.aureus* 6/12 (50)
Foreign	26/35 (74%)	35/35	34/35 (97%)		Enterococcus 5/5
Carbenicillin	19/27 (70%)	25/27 (93%)	23/28 (82%)		
US Study	10/14 (71%)	13/14 (93%)	12/15 (80%)		
Foreign	9/13 (69%)	12/13 (92%)	11/13 (85%)		
[redacted]					

°Comparator in study shown indented
EOT=End of Therapy; EOS=End of Study
♦Success includes cure + improvement
* Non-enterococcal gram-positive not evaluable in these trials
+ Clinical cure and improvement at long-term follow-up
• Assessed at 1-6 month follow-up

MO Comment: Microbiologic eradication rate for subject's infection ranged from 70%-96% among quinolone studies submitted to the FDA seeking the indication of bacterial prostatitis. Clinical cure ranged from 69%-91%, with a predictable decrease in cure rates to 55%-79% in the long-term follow-up period. However, it should be noted, that differences in trial design and endpoints make comparisons and pooling difficult. *E.coli* was the most common organism isolated.

NDA 19-537/Ciprofloxacin for CBP

NDA 19-537 consisted of eight studies conducted from 1984-1993. Four prospective studies were accepted by the reviewing MO as having appropriate data, one was a US trial, three were conducted in Germany and one in the Netherlands. All four had a period of treatment of 28 days with ciprofloxacin with comparators including TMP/SMX and carbenicillin, one trial

had no comparator. Data from these trials were pooled to obtain integrated efficacy results. Eradication of admission pathogen for ciprofloxacin was 72/89 (81%).

MO Comment: These studies were similar to CAPSS-101 in their inclusion criteria, diagnosis of CBP, and primary outcome. Microbiological eradication was assesed either at the one-month or three-month follow-up visit. CAPPS-101 assessed microbiological eradication at the 5-19 day posttherapy visit. Unlike CAPPS-101, no gram-positive organisms were allowed except for enteroccoci.

NDA 19-735/Ofloxacin for bacterial prostatitis:
Ofloxacin had a clinical cure rate of 79% at long-term follow-up compared to a 53% clinical cure rate for carbenicillin. Cure plus improvement resulted in an overall cure rate of 86% for the ofloxacin-treated patients and 78% for the carbenicillin-treated patients. The eradication rates at the first post-therapy visit were 75% for ofloxacin versus 67% for carbenicillin. There was a 0% and 11% reinfection rate per arm, respectively.

All patients on the ofloxacin arm of the study had an infection with a single organism. The most commonly isolated pathogen was *Escherichia coli* (15/33), followed by *Proteus mirabilis* (4/33), and *Pseudomonas aeruginosa* (4/33). The respective numbers for the carbenicillin patients were 14/33, 5/33, and 1/33. *Enterococcus faecalis* was also seen in 4/33 of the carbenicillin patients and none of the ofloxacin patients. Coagulase-negative staphylococci were considered evaluable in 1/33 isolates on each arm.

MO Comment: This study was similar to CAPPS-101 in its requirement for symptoms and positive culture for inclusion into the trial. However primary outcome of microbiological eradication was assessed at 4-6 weeks posttherapy and at the 5-19 day posttherapy visit in CAPPS-101.

NDA 20-043/Temofloxacin for prostatitis

This study was an uncontrolled, multicenter study. By protocol, patients were excluded if a gram-positive bacterium other than Enterococcus was isolated. Patients were evaluated 5-9 days after completion of therapy. Inclusion criteria were males, 18 years of age or over, positive culture, and symptoms. Eradication was 73/78 (93.6%) at the test-of-cure (TOC) visit, and 100% among the 9 *S.epidermis* isolates in the trial.

MO Comment: This study was similar to CAPSS-101 in its inclusion criteria, duration of therapy and timing of TOC visit. Although a violation of protocol, the S.epidermis isolates were accepted by the reviewing MO; it is not clear whether these represented pure isolates.

NDA 20-759/Trovafloxacin for chronic bacterial prostatitis

This study was controlled, multicenter, randomized, blinded study with a trovafloxacin regimen of 28 days. The primary efficacy variable was clinical efficacy at the TOC with trovafloxacin 62/68 versus ofloxacin 51/58. The 95% **CI was –9.1%, 15.6%** (Δ10) for trovafloxacin minus ofloxacin, thus establishing clinical equivalence. For the secondary efficacy outcome of bacteriological efficacy at the end-of-therapy (EOT) trovafloxacin did not meet delta of 15 [70.4% (38/54) vs. comparator 80.0% (28/35)]. A delta of 20 was imposed for end-of-study (EOS) clinical evaluations which trovafloxacin met. The most commonly isolated pathogen was *E.coli*; ten pure *S.epidermis* isolates were included in this trial with an eradication rate of 80%. The reviewing MO, Dr. Regina Alivisiatos, accepted *S.epidermis* as a pathogen. The number and quality of the cases were felt to be sufficient to grant the indication of *S.epidermis* CBP along with *E.coli* and *Enterococcus faecalis*. Five patients discontinued trovafloxacin due to increased liver function tests that were considered treatment related.

MO Comment: This study had similar inclusion, diagnostic criteria, and evaluation times as CAPSS-101. However, the primary efficacy variable was clinical outcome in the trovofloxacin study and bacteriologic outcome in this current NDA. A delta of 15 was used for the primary efficacy variable in the trovafloxacin NDA. Elevations in liver function tests were seen in the trovafloxacin-treated patients which was found to be associated with hepatic failure in postmarketing surveillance.

Major issues that arose during clinical trial, for example, study design, safety, or ethical considerations.

No major issues arose during CAPPS-101.

1.4. Other Relevant Information

LEVAQUIN® sponsored by The R.W. Johnson Pharmaceutical Research Institute was first approved in the US on December 20, 1996.

Text in Italics from **Applicant's submission**

To our knowledge no regulatory body has refused drug approval for safety reasons and no warning letters to physicians have been distributed regarding this product.

1.5. Important Issues with Pharmacologically Related Agents

Some quinolones cause QT prolongation, but the impact of this clinical finding is unclear. Grepafloxacin was withdrawn from the US market secondary to seven serious cardiac events, including torsades de pointe. Concerns about the long-term effects on bones/joints in juvenile animal models have precluded the approval of fluoroquinolones for the pediatric population. The only approved quinolone for use in pediatrics is ciprofloxacin for the indication of post-exposure inhalational anthrax.

Liver enzyme abnormalities are seen in about 2% of patients who receive a fluoroquinolone. Serious hepatoxicity was observed with trovafloxacin regimens longer than 2 weeks and this led to change in labeling limiting the scope of its use.[3]

Serious adverse events were reported for temafloxacin an oral fluoroquinolone approved in 1992. Temafloxacin was withdrawn from the market because it was associated with a syndrome characterized by hemolytic anemia, likely immune mediated, in some cases accompanied by renal dysfunction, DIC (disseminated intravascular coagulation), neurological symptoms. This syndrome resulted in two deaths[4].

2. Significant Findings From Chemistry, Animal Pharmacology and Toxicology, and Microbiology

Chemistry This application may be approved from the Chemical Manufacturing and Controls (CMC) perspective after the labeling is updated to reflect change in the established name for the [redacted] For **details, please refer to Dr. Gene Holbert's review**

[3] Fish DN. Fluoroquinolone Adverse Effects and Drug Interactions. Pharmacotherapy 2001;21(10 Pt 2):253S-72S.

[4] Blum MD, Graham DJ and McCloskey CA. Temafloxacin Syndrome: Review of 95 cases. Clin Infect Dis 1994;18:946-50.

Animal Pharmacology and Toxicology No new animal pharmacology data were submitted with this application; nonclinical pharmacology and toxicology **studies were previously submitted under IND's 36,627 and 38,683. These** studies supported clinical trials for CBP at the dose level and duration sought in the proposed indication. The NDA submission is approvable from the perspective of nonclinical pharmacology and toxicology and no additional nonclinical studies are required. The label for this section is acceptable. For **details, please refer to Dr. Stephen G. Hundley's review.**

Microbiology The supplemental application is approvable from the microbiological viewpoint with changes recommended to the label taken into **account. For further details, please refer to Dr. Peter A. Dionne's review.**

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics (PK)

The Applicant submitted CAPSS-034 with this submission for CBP.

CAPSS-034 This Phase 1 study evaluated tissue penetration of levofloxacin 500mg into the prostate of men undergoing transurethral prostatectomy for benign hypertrophy. Population pharmacokinetic modeling was performed in this study. Prostate-to-plasma penetration ratio is 3.24 (calculated from the mean parameters). Prostate levofloxacin concentrations are higher, on average, than those in serum. In the non-inflamed prostate, levofloxacin achieves intracellular concentrations above minimal inhibitory concentrations. **For more details please refer to Dr. Phil Colangelo's review.**

The material in this section is from the most current Levofloxacin label

Background

- Basic PK properties

  Levofloxacin has an absolute bioavailability of 99% after a 500mg and 750mg oral dose.

  A 500-mg intravenous dose of levofloxacin infused over 60 minutes, results in a mean ± standard deviation (SD) peak plasma concentration of 6.2 ± 1.0 µg/mL.

  Levofloxacin's pharmacokinetics are linear and predictable. Steady-state is reached within 48 hours following a 500-mg or 750-mg once daily dosing regimen.

  This drug undergoes limited metabolism in humans. Levofloxacin is largely excreted unchanged in the urine with a mean terminal plasma elimination half-life ranging from 6-8 hours.

- Potential for interactions as substrate, inhibitor, inducer

marked than with other quinolones. However, sucralfate, antacids and multivitamins (containing magnesium, aluminum, iron, or zinc) may interfere with gastrointestinal absorption of LEVAQUIN® Tablets. No significant interactions with theophylline, warfarin, cyclosporine, digoxin, probenecid and cimetidine have been identified. 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.

- Effects of impaired renal and hepatic function

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50 mL/min). Pharmacokinetic studies in hepatically impaired patients have not been conducted. However, because of its limited metabolism the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

- Effects of gender, race

There are no significant differences in pharmacokinetics between male and female patients. The apparent total body clearance and apparent volume of distribution were not affected by race.

3.2. Pharmacodynamics (PD)

No new pharmacodynamic studies were submitted with this application.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

J&J's submission for NDA 20-634 included clinical data from study CAPSS-101 which was a multi-center, double-blind study comparing the safety and efficacy of levofloxacin to that of ciprofloxacin in the treatment of CPB.

Overview of Clinical Trials

One trial was submitted to support this indication, CAPSS-101

4.2. Postmarketing Experience

The material in this section is from the most current Levofloxacin label

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.

4.3. Literature Review

Classification

Prostatitis is a range of syndromes that encompasses acute bacterial prostatitis, chronic bacterial prostatitis, non-bacterial prostatitis and prostatodynia. This classification system devised by Drach et al is based on the presence of leukocytes and bacteria, chronicity and symptom assessment.

The National Institute of Health has proposed a new classification system:
Category I Acute Bacterial Prostatitis = Acute Infection of the prostate gland
Category II Chronic Bacterial Prostatitis = Recurrent infection of the prostate
Category III: Chronic Abacterial Prostatitis/CPPS: No demonstrable infection
A: Inflammatory CPPS = WBCs in semen/EPS/VB3
B: Noninflammatory CPPS = No WBCs in semen/EPS/VB3
Category IV: Asymptomatic Inflammatory Prostatitis

This classification takes into account the presence of infectious markers such as bacteria and leukocytes and symptom presence or absence. In CAPPS-101 CBP was defined by recurrence of infection as in the NIH classification and presence of symptoms and positive bacterial cultures. The complexity of this scheme underlines the difficulty encountered by clinicians treating this illness.

There is a need for a consensus classification and clearer definitions of prostatitis to prevent overlap of syndromes. Although acute bacterial prostatitis is easily diagnosed and treated, the same is not true of CBP. Patients with chronic prostatitis are often empirically diagnosed and treated[6].

Etiology

The same bacteria that cause urinary tract infection cause CBP and one theory is that they are acquired through the urethra in an ascending manner[5]. Other theories of acquisition of infection in CBP are easy reflux of urine secondary to ductal anatomy in the peripheral zone of the prostate gland or a secretory dysfunction both leading to bacterial entry into the gland[6].

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[5] Nickel JC. New concepts in the pathogenesis and treatment of prostatitis. Current Opinion in Urol. 1992; 2:37-43

[6] Roberts RO, Lieber MM, Bostwick DG and Jacobsen SJ. A review of clinical and pathological prostatitis syndromes. Urology. 1997; 49(6): 809-821.

The etiologic agent in acute and chronic bacterial prostatitis is *Escherichia coli*, followed by Proteus and Providencia, with some cases being caused by Klebsiella, Pseudomonas, Serratia and Enterobacter. Enterococci are thought to be pathogens of minor importance, and the role of other gram-positive cocci is controversial[7]. Weidner et al studied 1461 patients with symptoms of chronic prostatitis from 1976-1988 and found that 97/1461 (6.6%) had bacteria isolated not including ureoplasma or chlamydia species. They divided their groups into four time periods taking into account differences in diagnostic techniques and practice, among these groups between 5.2%-10.2% of patients had chronic bacterial prostatitis. *E.coli* was the most common bacteria isolated found in 65% (64/97) of cases in which a bacteria was isolated. Other bacteria isolated include enterococcus in 18/97 (18.6%), other gram-negative bacteria in 8/97 (8.3%), and other gram-positive bacteria in 7/97 (7.2%) including *Staphylococcus saprophyticus* and streptococci[8].

In contrast a study submitted by the Applicant and conducted in the 1990s in China had a preponderance of gram-positive bacteria as opposed to gram-negative bacteria as is usually found. Patients with a clinical diagnosis of chronic bacterial prostatitis who had leukocytosis on prostatic fluid specimens had 107/138 isolates on prostatic fluid specimen. The most common pathogenic bacteria found were *Staphylococcus aureus* (48/107), enterococci (15/107), *E.coli* (12/107), *K.pneumoniae* (8/107) and *Staphylococcus epidermis* (6/107). Among positive cultures 5/107 were positive for *N.gonorrhoeae* and 4/107 for *C.albicans*[9].

Pathogenesis

In animal models prostatitis can be induced by insertion of catheter into the urethra followed by injection of a bacterial suspension with 100% infection rate. About half of the animals clear this infection, however in the remaining half this leads to a chronic process. This process is characterized by fibrous tissue proliferation and acinar regression with some areas becoming heavily infiltrated by lymphocytes with few bacteria. Bacteria exist as microcolonies adherent to the prostatic duct and acinar wall rather than the interstitium, which although sparse are immunogenic. Circulating antigen-antibody

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[7] **Lipsky BA. Prostatitis and Urinary Tract Infection in Men: What's New; What's True?** Am J Med. 1999; 106: 327-34.

[8] Weidner W, Schiefer HG, Krauss H, Jantos Ch, et al. Chronic Prostatitis: A Thorough Search for Etiologically Involved Microorganisms in 1,461 Patients. Infection. 1991;19(Supp 3):S119-25.

[9] Shaohua P, Jianhua Y, Xuemei S and Jianzhui L. An Etiological Study and Investigation of Drug Susceptibility in Chronic Bacterial Prostatitis. Acta Academiae Medicinae Hubei. 1996; 17(4): 388-90.

immune complexes are found in animals with chronic bacterial prostatitis[10]. In experimental CBP deposition of antibody along the basement membranes of the prostatic ducts occurred early in infection and creates a chronic inflammatory state. Similarly, in patients with CBP antigen-specific IgA and IgG in serum are normal but both IgA and IgG are elevated in prostatic fluid[11].

Diagnosis

On digital rectal examination, the prostate is frequently normal but may be tender, boggy, swollen or firm[6]. Examination of expressed prostatic secretions has been the definitive test for diagnosing prostatitis since Meares and Stamey introduced the "four-cup" prostatic localization test. This test has never been validated[7].

Although serial urines are recommended very few patients actually are cultured in clinical practice. CBP is challenging to diagnose, treat and tends to recur which might due to the presence of bacteria microcolonies or biofilms. The contribution of the immune system to this syndrome remains undetermined[5].

5. CLINICAL REVIEW METHODS

5.1. Describe How Review was Conducted

One pivotal trial was submitted by the applicant, CAPSS-101 which was reviewed in detail. Postmarketing data collected by the Applicant was used in the Applicant's integrated safety analysis.

The Medical Officer reviewed inclusion, exclusion criteria, patient assessments, evaluability; and clinical and microbiologic outcomes.

The submitted electronic case report forms (CRF) and narratives were reviewed by MO to verify inclusion and exclusion criteria, evaluability and outcomes. In addition, a random sample of 10% of cases from CAPSS-101 were reviewed. Minor differences in assessment were found but were felt to be unlikely to affect overall conclusions. A few discrepancies existed between clinical investigator's clinical outcome assessment and MO in which the clinical investigator had deemed somebody a clinical cure and the MO felt it should have been an clinical improvement. Of note, is that in these instances the Applicant had same assessment as MO, however per protocol it was the clinical investigator who had the final decision. In all these instances, the Applicant had queried the clinical investigator and the investigator had felt that their initial assessment was correct. Most discrepancies surrounded the persistence of certain symptoms or appearance of symptoms which were felt

[10] Nickel JC, Olson ME, Costerton JW. Rat Model of Experimental Bacterial Prostatitis. Infection. 1991:19:S126-S130.

[11] Meares EM Jr. Prostatitis. Med Clin North Am. 1991;75:4-5-24.

by clinical investigator to be part of baseline symptoms. The reviewing MO felt that it was appropriate to allow the final decision to remain with the clinical investigator who was familiar with patient's baseline symptoms.

5.2. Overview of Materials Consulted in Review

- Electronic NDA 20-634 and NDA 20-635 folders
- MOR NDA 19-384 S 020 (norfloxacin), NDA 19-537 S021 (ciprofloxacin), NDA 20-043 (temafloxacin), NDA 20-759 (trovafloxacin), and the divisions director's review of NDA 19-735 (ofloxacin).

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI Inspection: On Jan 23rd, 2003 the Division of Scientific Investigations inspected the site for principal investigator Dr. Paul Ray in Chicago, Illinois. The records for all 43 enrolled patients were inspected. All patients consented to the trial. Overall assessment was VAI. Minor deviations from the regulations were found but the data were acceptable.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The Applicant states that CAPPS-101 was conducted in accordance to accepted ethical standards. The study was conducted under the requirements outlined in current Good Clinical Practices, Title 21 Part 56 of the Code of Federal Regulations pertaining to Institutional Review Boards, "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects" and with Title 21 Part 50 of the Code of Federal Regulations section pertaining to informed consent.

5.5. Evaluation of Financial Disclosure

The Applicant's Certificate of Financial Disclosure is in accordance with the Agency regulations 21 CFR 54.2 Form 3454. J&JPRD who is submitting this study on behalf of Ortho-McNeil Pharmaceuticals, Inc. certified that the listed clinical investigators did not participate in any financial arrangement with the Applicant. Only one sub-investigator had reportable equity interests in excess of USD 50,000. It was the Applicant's assessment that "there was no evidence that the investigator with a financial interest biased the result of the study".

MO Comment: The investigator with the financial interest was one of seven sub-investigators, in a site that enrolled four patients into each arm of the ITT population. **It is the judgement of this reviewer that this investigator's** impact on the trial was minimal

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The applicant submitted one pivotal study CAPSS-101.
Please see section 6.3 for details.

6.2. General Approach to Review of the Efficacy of the Drug

The Applicant's submission for NDA 20-634 includes one clinical study for the treatment of CBP, please see sections below for details.

Detailed Review of Trial by Indication

6.2.1. Indication. Chronic Bacterial Prostatitis

6.2.1.1. Applicant's protocol # CAPSS-101. A multicenter, double-blind study to compare the safety and efficacy of levofloxacin to that of ciprofloxacin in the treatment of chronic prostatitis. This study was conducted from May 4, 2000 to November 13, 2001.

6.2.1.1.1. Protocol . CAPSS-101

6.2.1.1.1.1. Objective/Rationale

The objective of this study was to evaluate the safety and efficacy of levofloxacin 500 mg administered orally (p.o.) once daily (q.d.) compared with ciprofloxacin 500 mg p.o. administered twice daily (b.i.d.) for a four-week course in the treatment of chronic bacterial prostatitis.

6.2.1.1.1.2. Overall Design
CAPPS-101 is a multicenter, double-blind, randomized, active controlled trial. This is a non-inferiority study with 82-92% power to test the null hypothesis assuming an 89% ciprofloxacin success rate with 87% for levofloxacin. The estimated number of microbiologically evaluable patients per group necessary was 55 to 77.

The Agency's Guidance for Industry on multicenter trials emphasizes the need for internal consistency within the study to prevent one center from having a large impact on the trial as a whole.

The study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the

effect, the credibility of the multicenter study is diminished.[12]

MO Comment: LEVAQUIN® may obtain the indication of CBP with a single statistically adequate and well controlled multicenter trial because it has been approved for the treatment of chronic urinary tract infection.

6.2.1.1.1.3. Population and Procedures

Inclusion Criteria

1) Males 18 years of age or older;

2) Clinical diagnosis of chronic prostatitis determined by the following three criteria:

- Clinical signs and symptoms of prostatitis including a soft, tender prostate without noticeable nodularity with one or more of the following: dysuria, suprapubic discomfort, painful ejaculation, low back pain, perineal discomfort, frequency, urgency, hesitancy and decreased urinary stream or urinary retention, pain on digital examination, perineal tenderness, fever or chills

MO Comment: The above inclusion criteria were verified by investigator upon enrollment. The above signs and symptoms were listed as a single item to which the investigator answered yes/no. Because of the manner in which these criteria were **grouped into one "yes/no" question in the CRF, it is difficult to know if the investigator was answering "yes" to the presence of prostate tenderness plus another symptom, or "yes" to only one of** the two required entry criteria. Please see section 6.2.1.1.2.1 Patient Disposition under sub-heading Clinical signs for more details on this issue.

- History of chronic prostatitis defined as one previous clinical diagnosis of prostatitis for a symptomatic episode that lasted at least four weeks or two or more other episodes of any duration during the previous twelve months; and
- Laboratory evidence of prostatitis
  - VB_3 specimen containing ≥10 times the WBC count of VB_2; restricted to three patients per investigational site initially, but could be increased at the Applicant's discretion;

[12] Guidance for industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products at http://www.fda.gov/cder/guidance/index.htm

- Patients who met this criteria could be enrolled immediately if the investigator felt the patient was too symptomatic to wait
- If a patient was randomized in the WBC stratum and was subsequently found to meet the microbiologic criteria the **patient's data was included in the microbiologically evaluable** population (MBE)

MO Comment: The reviewing MO verified all admission cultures for patients who were initially enrolled as part of the WBC stratum but were later found to meet microbiologic criteria. No discrepancies were found and the reviewing MO felt that these patients were appropriately included in the MBE population.

- **Data from patients enrolled based on the presence of WBC's** that do not meet the criteria of bacterial prostatitis were to be included in the non-bacterial prostatitis population for analysis

– VB_3 or EPS specimen containing $\geq 10^2$ CFUs of a single bacterial strain if the VB_2 specimen was sterile;
– VB_3 or EPS specimen containing ≥10 times the bacterial count (CFUs) of VB_2;
– VB_3 or EPS specimen containing $\geq 10^2$ bacterial count of a bacterial strain that was different from any present in VB_2 and was recognized as a uropathogen;

MO Comment: WBC count is not a recommended diagnostic technique as the primary outcome is microbiologic. Patients who only met WBC criteria were not included in MBE population and were analyzed separately by the Applicant. The other three criteria are consistent with **the Agency's draft guidance on prostatitis.**

Exclusion Criteria

- Received an experimental drug or used an experimental medical device within 30 days prior to screening
- Required parenteral therapy for the treatment of prostatitis
- Admission pathogen known or suspected to be resistant to either study drug
- Allergic response(s) to levofloxacin, ofloxacin, ciprofloxacin, or other members of the quinolone class of antibacterials
- Received recent therapy (within the last 14 days) with a quinolone for any reason
- Calculated creatinine clearance below 50 ml/min
- Grossly underweight (≤40 kg)
- More than 24 hours of potentially effective therapy within the seven days prior to study entry, unless there was documented evidence of

an organism resistant to that therapy or clinical failure after five or more days of previous antibacterial therapy

- Required a second systemic antibacterial regimen
- Previously treated under this protocol
- Any condition that could interfere with the evaluation of study drug, including the following: transurethral prostatectomy within six months of enrollment, the presence of a permanent transurethral catheter, or a history of cystostomy or nephrostomy
- Taking medication that could affect bladder or prostate function (e.g., hormone therapy, anticholinergics, or alpha-blockers)
- Known prostatic carcinoma
- Clinical contraindications (e.g., unstable angina) for participation in the study
- Another infection requiring therapy with an antibacterial agent other than the study drug

Concomitant Therapy

Administration of nonstudy systemic antibacterials was prohibited. Patients were to discontinue medications that contained divalent or trivalent cations. Patients on sawpalmetto were to continue this therapy at the same dose throughout the study.

Other over-the-counter medications were to be continued at the same dose throughout the study. Antacids were to be ingested two hours or longer before or after the study medication.

Study medication

All patients were to receive two capsules each day for 28 days as appropriate, so that patients randomized to levofloxacin received levofloxacin q.d. (with identical placebo capsules balancing the blind), and patients randomized to ciprofloxacin received ciprofloxacin b.i.d.

Procedures

Procedure/Assessment	Visit 1 Screening	Visit 2 Admission Day 1	Visit 3 On-therapy Day 7-10	Visit 4 Week 3 Day 21-26	Visit 5 Posttherapy Day 33-40	Visit 6 Poststudy Day 52-63	Visit 7 6-Month Follow-up
Informed Consent	X						
Medical History	X						
Pertinent Physical Exam		X	X		X		
Vital Signs		X	X		X		
Height and Weight		X					
Clinical Signs and Symptoms		X	X		X	X	
Prostatitis Symptom Assessment Instrument		X		X	X		
Culture and Microscopic Evaluation	X		X		X	X	
Hematology		X			X		
Chemistry		X			X		
Urinalysis		X			X		
Dispense/Account for Study Drug		X	X		X		
Concomitant Medication Query		X	X	X	X		
Assess Adverse Events		X--------	----------	X----------	X--------		
Relapse Assessment							X

Adapted from Table 1 of CAPSS-101 Study Report

MO Comment: As part of the protocol, the Applicant conducted a telephone interview during Visit 7. This data was not submitted with this NDA.

6.2.1.1.1.4. Evaluations/Endpoints

Endpoints

The primary efficacy endpoint was microbiologic response of each **patient's infection at the posttherapy visit (5-18 days after completion of** treatment) for the microbiologically evaluable group.

MO Comment: This is consistent with FDA's guidance for prostatitis.

Secondary efficacy variables included:

- The posttherapy microbiologic response by pathogen identified at admission
- The one-month poststudy (24-45 days after completion of therapy) assessment of microbiologic relapse by patients' infections, for patients who were cured or improved at the posttherapy visit
- The one-month poststudy assessment of microbiologic relapse by pathogen identified at admission, for patients who completed therapy and were cured or improved at the posttherapy visit
- Clinical cure posttherapy

- Clinical success (cured or improved) posttherapy
- The resolution and improvement of clinical signs and symptoms from admission to posttherapy, as assessed by the investigator
- The transition in scores on the prostatitis symptoms index from admission to posttherapy
- The one-month poststudy clinical success for patients who completed therapy and were cured or improved at the posttherapy visit

Blinding
CAPPS-101 was double-blinded. To maintain the blind, the active study drugs and placebo were encapsulated in identical-appearing capsules and packaged in identical containers.

6.2.1.1.1.5. Statistical Plan

The sample size for this study was calculated by Applicant to provide a sufficient number of patients to show that levofloxacin is as effective as ciprofloxacin for CBP with a delta of 20% for microbiologic efficacy.

6.2.1.1.1.6. Analysis Populations

Intent-to-Treat Population
The intent-to-treat (ITT) population was defined as all randomized patients who received at least one dose of study medication.

Safety Evaluable Population
The safety evaluable population was defined as patients who received at least one dose of study drug and for whom safety information was available after the initial dose.

Modified Intent-to-Treat Population
The modified intent-to-treat (MITT) population was defined as all ITT patients who were found to have an admission pathogen and were randomized, regardless of whether they were randomized based on microbiologic or the WBC criteria.

Microbiologically Evaluable Population
The microbiologically evaluable population (MBE) was defined as patients who fulfilled the protocol-specified clinical and microbiologic evaluability criteria. This population could include patients randomized based on either the microbiologic or the WBC criteria, and if enrolled based on WBC criteria, were later found to have an admission pathogen.

Nonbacterial Evaluable Population
The nonbacterial evaluable population was defined as patients who were enrolled based on WBC criteria and did not have an admission pathogen.

6.2.1.1.2. Results

6.2.1.1.2.1. Patient Disposition

List of Investigators
A total of 383 patients were enrolled in this study by 65 investigators at 65 centers in the United States. See Appendix 1 for list of investigators and center enrollment.

Populations

Population	Levofloxacin	Ciprofloxacin	Total
Enrolled	199	184	383
ITT	197	180	377
Safety	197	180	377
MITT	170	151	321
MBE	136	125	261

MO Comment: In this table the reader can appreciate that the ITT population is the same population that was used for the safety analysis. The MBE is a subset of the ITT population and is the population in which the primary outcome was evaluated.

Attrition from Enrolled Population
Six patients from the enrollment population, two in levofloxacin arm and four in the ciprofloxacin arm did not receive any study drug and were not included in the ITT population.
(Patient numbers 46935, 94902 in the levofloxacin arm. Patient numbers 46927, 46929, 49904 and 65901 in the ciprofloxacin arm.)

MO Comment: No information as to reasons for withdrawal from the trial was given. These patients did not receive any study drug and therefore their outcomes would not be applicable to efficacy or safety.

Attrition from the ITT Population

A total of 56 patients, 27 patients in the levofloxacin arm and 29 patients in the ciprofloxacin were excluded from the MITT population. These patients were excluded because they did not have an admission pathogen. Patient numbers are shown in Appendix 2.

Among the ITT population, a similar number of patients in each study arm discontinued therapy, 25 in the levofloxacin arm and 27 in the ciprofloxacin arm. For details on reasons for withdrawal see section Completion/Withdrawal.

MO Comment: There are some small differences in the reasons for discontinuation of drug therapy but the numbers are too small to draw any conclusions; the overall rate of discontinuation is similar between the two arms of the study.

Attrition from the MITT population

A total of 60 patients, 34 in the levofloxacin arm and 26 in the ciprofloxacin arm were excluded from the MBE population. In the levofloxacin arm, the most common reason for exclusion was insufficient therapy (13/34) followed by no posttherapy culture done at the appropriate window (10/34). In the ciprofloxacin arm, the most common reason for exclusion was no post-therapy culture done at the appropriate window (10/26) followed by insufficient therapy (7/26).

The remainder of the patients were excluded for reasons such as: course of therapy too long, lost to follow-up, admission culture not done at the appropriate window, and one protocol violation. The protocol violation involved a patient with creatinine clearance <50 ml/min in the levofloxacin arm.

Primary Reason For Microbiologic and Clinical Nonevaluability MITT population

	Levofloxacin (N=197)[a]		Ciprofloxacin (N=180)[a]	
	n	(%)	n	(%)
Total no. of microbiologic patients (modified ITT)[b]	170		151	
Microbiologically evaluable population	136	(80.0)	125	(82.8)
Excluded from MBE population	34	(20.0)	26	(17.2)
Insufficient course of therapy	13	(7.6)	7	(4.6)
Course of therapy too long	3	(1.8)	5	(3.3)
Effective concomitant therapy	0	(0.0)	0	(0.0)
Lost to follow-up	2	(1.2)	2	(1.3)
Admission culture not within 5 days pretherapy	5	(2.9)	2	(1.3)
No posttherapy culture between Days 5-18	10	(5.9)	10	(6.6)
Other protocol violation	1	(0.6)	0	(0.0)

[a] Patients were counted only once according to the hierarchical ordering of reasons.
[b] Includes all ITT patients who had at least one admission pathogen
Adapted from Table 9 of CAPSS-101 Study Report

MO Comment: This table in the Applicant's submission was reproduced by MO using Applicant's dataset and there were no discrepancies. The categories above were used to exclude patients who did not meet the **Applicant's criteria for inclusion into the MBE population. Events such as** death, clinical failure, adverse events are not listed above because these were not used by the Applicant to exclude patients from microbiologic evaluability. Patients included in the insufficient therapy category are listed below. One death in the levofloxacin arm falls under this category. Similarly, five patients in the levofloxacin arm discontinued due to an AE compared to four patients in the ciprofloxacin arm these patients are listed under this category as well. Two patients who chose to withdraw from the study in the levofloxacin arm. These two patients were not clinical failures and did not have an AE. The category of insufficient therapy also includes one patient in each arm of the study who were withdrawn from study when they were found to have resistant organisms. Additionally, one patient in the levofloxacin arm whose labs were delayed for 21 days and one patient whose baseline labs were found to be abnormal in the ciprofloxacin arm are also included. Please refer to completion/withdrawal section for details on reasons for withdrawal from study.

Demographics

Demographic and baseline characteristics of the ITT population are listed in Table below. The mean age for the patients was 51.2 years (18-83 years). Most patients were Caucasian (74.3%).

Demographic Characteristics of ITT population		
	Levofloxacin (N=197)	Ciprofloxacin (N=180)
Age (mean ±SD)	50.9 ± 14.67	51.5 ± 15.15
Race		
Caucasian	146 (74.1%)	134 (74.4%)
Black	24 (12.2%)	24 (13.3%)
Asian	3 (1.5%)	3 (1.7%)
Other	24 (12.2%)	19 (10.6%)
Weight (kg)	87.9 ± 16.08	87.8 ± 16.87

MO Comment: Prostatitis is diagnosis of adult males. A study that analyzed office visits by males from 1990-1994 found that prostatitis was more commonly diagnosed in men 36-65 years old than those 18-35 years old[13]. The age range and mean of the study patients is thus appropriate.

Clinical Characteristics

Clinical Signs

Most patients in the trial did not have fever (97.3%) or rigors (98%). About 74% of the patients had mild/moderate prostate tenderness. Half the patients had no perineal tenderness and those with tenderness mostly had mild symptoms. Please refer to Appendix 3 for specifics.

MO comment: Clinical signs at admission were similar in the two study arms of the ITT population. Review of clinical signs of the ITT population elicited 56 patients (31 levofloxacin patients, 25 ciprofloxacin patients) who had no prostate tenderness and 18 patients who were labeled unknown (9 in each arm of the study) at admission (Visit 2). The review team requested information from the Applicant about these patients, as prostate tenderness was one of the required criteria for inclusion into the trial. The Applicant replied that all 72 patients, the 56 without prostate tenderness and the 18 unknown patients, had prostate tenderness detected at screening (Visit 1). In the CRF for the screening visit all inclusion criterion were listed as a single item and all subjects in the ITT population were marked as satisfying this criterion. The MO verified this and found that all patients had met inclusion **criteria at screening per the Applicant's dataset.**

[13] **Collins MM, Stafford RS, O'Leary MP, and Barry MJ. How common is prostatitis? A** national survey of physician visits. The Journal of Urology. 1998;159(4):1224-8.

MO Comment (continued): The Applicant performed a review of cases where screening and admission were conducted on the same date to determine if any of the cases had a discrepancy between the response to inclusion criterion at screening and the response to **prostate tenderness at admission, to address the review team's** inquiry. For the admission visit, in the CRF, symptoms and signs were listed separately. Presumably, for patients who had these visits on the same date, there should be consistency between the two visits. For 74 patients, the two visits occurred on the same date, discrepancy was found in 6/74, however only one of these six cases was included in the MBE population. This case met microbiologic criteria and had symptoms of CBP. It is possible, that patients who had prostate tenderness at admission might have resolved this symptom after examination at screening since prostate massage can relieve pressure and alleviate pain. Although the number of discrepancies found were small it reinforces the flaw in grouping together a list of inclusion criterion in the CRF. Two analyses were performed by MO to resolve this issue. The patients without tenderness were analyzed separately. In addition, since half of the 56 patients without prostate tenderness at admission came from Center 7, an analysis of the efficacy results for this center versus the other centers was performed. Because of the small sample size no conclusions could be drawn on the trends observed and these patients were included in the overall **analysis. Please see section "Other sub-analysis" under this section** for details.

Clinical Symptoms

Most of the patients did not have fever or rigors documented at admission. Over half of the patients in the trial had mild/moderate severity of one or more of the following: dysuria, frequency, urgency, hesitancy, low back pain, perineal discomfort, decreased urinary stream and sense of incomplete voiding. Please refer to Appendix 4 for specifics.

MO Comment: The distribution and severity of clinical symptoms in the ITT population were similar in both study arms.

Protocol Violations and Concomitant Medications
A total of 64 protocol deviations were recorded.

	Levofloxacin	Ciprofloxacin
Protocol Deviations	28	36
Concomitant medications	20	27
Resistant Organisms	4	5

MO Comment: None of the protocol waivers for concomitant medications were granted for antibiotics. Concomitant medications included CARDURA®, HYTRIN®, FLOMAX®, PROSCAR® and testosterone among others. These medications had to be continued at the same dose throughout study. Though they might have impacted symptoms, this effect was to be minimized by maintaining baseline dose and by only granting waivers to medications used chronically. The primary outcome of this trial was microbiologic eradication, which would not be affected by these concomitant medications.
A total of 9 patients, 4 in the levofloxacin arm and 5 in the ciprofloxacin arm, with resistant organisms were admitted for which a waiver was obtained from Applicant so enrollment could proceed. NOTE: Other patients who were found to have resistant organisms could remain in the trial if they showed improvement at visit 3.

Compliance

Duration of Therapy*	Levofloxacin	Ciprofloxacin
22-28 days	149/197 (75.6%)	131/184 (72.8%)
>28 days	23/197 (11.7%)	24/184 (13.3%)

*In ITT population

MO Comment: At least 80% and no more than 120% of the treatment regimen was to be taken by subjects in order to qualify for the microbiologically evaluable population.

Completion/Withdrawal

Study Completion/Withdrawal Information: Randomized Patients

	Levofloxacin		Ciprofloxacin	
Patient disposition	n	(%)[a]	n	(%)[a]
Total randomized	199		184	
Intent-to-treat	197		180	
Total who withdrew from therapy	25	(12.7)	27	(15.0)
Primary reason for premature withdrawal during therapy				
Adverse event	10	(5.1)	8	(4.4)
Clinical failure	3	(1.5)	4	(2.2)
Patient's decision	2	(1.0)	4	(2.2)
Protocol violation	0	(0.0)	0	(0.0)
Lost to follow-up	5	(2.5)	3	(1.7)
Death	1	(0.5)	0	(0.0)
Other	4	(2.0)	8	(4.4)
Total completing therapy	172	(87.3)	153	(85.0)
Total eligible one-month poststudy evaluation[b]	134		125	
Total completing one-month poststudy evaluation[b]	118		107	

[a] Percentages are based on number of ITT patients.
[b] Patients clinically cured or improved and completed therapy at the posttherapy visit. They were to be followed for one month and six months posttherapy
Adapted from Table 7 of CAPSS-101 Study Report

MO Comment: A total of 87.3% of ITT patients in the levofloxacin-treatment group completed therapy compared to 85.0% in the ciprofloxacin-treatment group. The most common reason for discontinuation in the levofloxacin group was an adverse event in 10/197, compared to 8/180 in the ciprofloxacin arm. In the **ciprofloxacin arm, 8/180 subjects discontinued due to "other"** reasons which included did not meet culture criteria, resistant organism, laboratory error, and abnormal laboratory values. Among the ITT population, equivalent numbers withdrew from therapy. Two serious AEs occurred in this study, subject 51903 in the levofloxacin arm died secondary to a hemorrhagic brain stem infarct not related to study drug, and subject 25903 had an episode of increased anxiety and depression not felt to be related by study drug. For details on AEs please see Section 7.4. A comparable number of patients in each arm of the study discontinued due to clinical failure. The balance in the number of attritions from the MBE population and the balance in the reasons support the validity of this study.

6.2.1.1.2.2. Efficacy Endpoint Outcomes

Data Set Analyzed
Patient enrollment by study center is included in Appendix 1. The MBE population was the population for primary efficacy, consisting of 136 patients in the levofloxacin arm and 125 in the ciprofloxacin arm.

Efficacy Endpoints

The primary efficacy endpoint was microbiologic response of each **patient's infection at the posttherapy visit (5-18 days after completion of** therapy) for the microbiologically evaluable group.

Secondary efficacy variables included:

- The posttherapy microbiologic response by pathogen identified at admission
- The one-month poststudy (24-45 days after completion of therapy) assessment of microbiologic relapse by patients' infections, for patients who were cured or improved at the posttherapy visit
- The one-month poststudy assessment of microbiologic relapse by pathogen identified at admission, for patients who completed therapy and were cured or improved at the posttherapy visit
- Clinical cure posttherapy
- Clinical success (cured or improved) posttherapy
- The resolution and improvement of clinical signs and symptoms from admission to posttherapy, as assessed by the investigator
- The transition in scores on the prostatitis symptoms index from admission to posttherapy
- The one-month poststudy clinical success for patients who completed therapy and were cured or improved at the posttherapy visit

Primary Efficacy Result
The primary efficacy endpoint was the microbiologic response at the posttherapy visit in the MBE population. 102/136 (75%) patients had baseline infections eradicated in the levofloxacin arm compared to 96/125 (76.8%) in the ciprofloxacin.

Microbiologic Response by Patient's Infections at Posttherapy

	Levofloxacin	Ciprofloxacin	
MBE	N=136	N=125	95% CI
Eradication	102 (75%)	96 (76.8%)	-12.58, 8.98
Persisted	34 (25%)	29 (23.2%)	
MITT	N=170	N=151	
Eradication	119 (70.0%)	109 (72.2%)	-12.44, 8.07
Persisted	51 (30.0%)	42 (27.8%)	

Adapted from Table 12 of CAPSS-101 Study Report

MO Comment: The microbiologic eradication was 75.0% in the levofloxacin arm and 76.8% in the ciprofloxacin (95% CI -12.58, 8.98) in the MBE population. This means that levofloxacin is no more than 13% less effective than ciprofloxacin in microbiologic eradication at the posttherapy visit (5-18 days after the completion of therapy). A delta of 20% was pre-specified for this endpoint which the Applicant met. This result was comparable to that encountered in the MITT population which had an eradication rate of 70% for levofloxacin and 72.2% for ciprofloxacin.

Secondary Efficacy Results

Posttherapy microbiologic response by pathogen

Pathogen Eradication Rates in MBE Population per Applicant

	Levofloxacin	Ciprofloxacin
	n/N (%)	n/N (%)
E.coli	14/15 (93)	9/11 (82)
E.faecalis	39/54 (72)	34/45 (76)
S.epidermis	20/24 (83)	26/29 (90)

MO Comment: Some patients had more than one organism isolated which met the criteria for a pathogen. Because of the difficulty of knowing which organism was the true pathogen when more than one organism was isolated, the reviewing medical officer did a sub-analysis of pure isolates. This analysis of pure isolates is especially important for organisms which are not established pathogens in CBP such as *S.epidermis*, [redacted] the trovafloxacin review for CBP, only pure isolates of *S.epidermis* were considered evaluable. Trovafloxacin was approved for *S.epidermis* CBP on the basis of 10 pure isolates.

Pathogen Eradication Rate for Pure Pathogens of Interest per MO

	Levofloxacin n/N (%)	Ciprofloxacin n/N (%)
E. coli	7/8 (87.5)	2/3 (66.7)
E. faecalis	18/23 (78.3)	18/23 (78.3)
*S. epidermidis**	9/11 (81.8)	11/14 (78.6)
[redacted]		

MO Comment: Eradication rates in the levofloxacin arm were comparable between all isolates as per Applicant analysis and pure isolates except for [redacted] For accepted pathogens, the reviewing MO felt comfortable considering pure and mixed isolates. Although the number of pure *E. Coli* is only eight, there were seven other cases in which *E.Coli* was found with a co-pathogen, the overall eradication rate was comparable between the pure and mixed infection. The efficacy of LEVAQUIN® in clinical infections and especifically in with *E. coli* has been established in uncomplicated and complicated urinary tract infections. The efficacy of LEVAQUIN® in clinical infections especifically in urinary tract infections has not been established for *S.epidermis* which is not a recognized established pathogen in CBP. For these reasons, in the case of *S.epidermidis* only pure isolates were considered. The eradication rate is adequate to approve LEVAQUIN® for the treatment of CBP due to *E.coli*, *E.faecalis* and *S.epidermis*. The number of isolates for [redacted] are too few to warrant approval.

Pathogen Eradication Rates for MBE Patients with Co-Pathogen(s) in the Levofloxacin Arm

	Eradication# n/N (%)	Top Co-Pathogen(s) Eradication n/N (%)
E. coli	7/7 (100.0)	*E.faecalis* 2/4 (50.0)
E. faecalis	21/31 (67.7)	*S.haemolyticus* 4/7 (57.0), *S.epidermis* 3/4 (75.0)
S. epidermidis	10/11 (90.9)	*E.faecalis* 2/4 (50.0)

MO Comment: The eradication rates among isolates found with other co-pathogens were similar to that seen with the Applicant analysis of all isolates. The most common co-pathogen was *E.faecalis*. *E.faecalis* was most commonly found with [redacted] and *S.epidermis*.

Clinical cure and success (cured + improved) at posttherapy

Clinical Cure and Success Rate at Posttherapy for Different Evaluable Populations

	Levofloxacin		Ciprofloxacin		
Clinical Cure Rate	n/N	%	n/N	%	95% CI
MBE	40/136	29.4	38/125	30.4	(-12.51, 10.53)
MITT	47/170	27.6	42/151	27.8	(-10.31, 9.98)
ITT	53/197	26.9	51/180	28.3	(-10.75, 7.89)
Clinical Success Rate					
MBE	102/136	75.0	91/125	72.8	(-8.87, 13.27)
MITT	122/170	71.8	107/151	70.9	(-9.34, 11.15)
ITT	138/197	70.1	125/180	69.4	(-8.96, 10.17)

The denominator for clinical response rates includes cure + improvement + failure + unable to evaluate.
Clinical Success includes cure + improvement
Adapted from Table 28 of CAPSS-101 Study Report

MO Comment: Clinical cure rate was 29.4% for the levofloxacin arm and 30.5% for the ciprofloxacin arm of the MBE population. Similarly, clinical cure rates in the MITT and ITT population were comparable between the two treatment groups. Clinical success rate which combines cure and improved categories, was 75% for the levofloxacin arm compared to 72.8% in the ciprofloxacin arm (95% CI [-8.87, 13.27]). Though, clinical success was not the primary efficacy end-point it is consistent with the rates of microbiologic success found in the primary outcome.

The resolution and improvement of clinical signs and symptoms from admission to posttherapy

Resolution of Clinical Signs and Symptoms Posttherapy in MBE Population

	Levofloxacin (N=136)	Ciprofloxacin (N=125)
Clinical Signs		
Fever	3/3 (100)	4/4 (100)
Rigor	0/1	2/3 (66.7)
Prostate Tenderness	57/110 (51.8)	59/103 (57.3)
Perineal Tenderness	43/56 (76.8)	39/53 (73.6)
Clinical Symptoms		
Dysuria	37/70 (52.9)	48/80 (60.0)
Frequency	36/107 (33.6)	43/109 (39.4)
Urgency	39/95 (41.1)	44/96 (45.8)
Hesitancy	36/79 (45.6)	35/85 (41.2)
Low Back Pain	36/75 (48.0)	27/81 (33.3)
Painful Ejaculation	35/56 (62.5)	33/51 (64.7)
Perineal Discomfort	47/81 (58.0)	37/78 (47.4)
Decreased Urinary Stream	36/77 (46.8)	36/87 (41.4)
Sense of Incomplete Voiding	38/89 (43.8)	30/83 (36.1)
Fever	8/10 (80.0)	8/8 (100.0)
Chills	6/7 (85.7)	11/12 (91.7)
Suprapubic Discomfort	48/72 (66.7)	28/58 (48.3)
Other	19/32 (59.4)	7/18 (38.9)

Adapted from Table 26 of CAPSS-101 Study Report

MO Comment: The rate of resolution is comparable between the two study arms for both clinical signs and symptoms. One patient with rigor in the levofloxacin-treatment arm had no resolution of this symptom. No conclusions can be drawn from this since all patients with fever did have resolution of this sign.

The transition in scores on the prostatitis symptoms index from admission to posttherapy

The proportion of patients with changes in prostatitis symptoms was similar in the two treatment groups.

Mean Changes in Score for Pain or Discomfort in Last Week

	Admission Mean ± SD	Posttherapy Mean ± SD	Change Mean ± SD
Levofloxacin	4.3 ± 2.47	2.6 ± 2.32	-1.7 ± 2.59
Ciprofloxacin	4.3 ± 2.32	2.7 ± 2.42	-1.6 ± 2.45

Pain based on 11 point scale, 0 (No Pain) to 10 (Pain as Bad as You Can Imagine)
Adapted from Applicant's Attachment 15H

MO Comment: Table above shows mean change in pain score from admission to posttherapy, in both arms of the study patients improved with a decrease in mean score for pain. For other specific symptoms both the levofloxacin and ciprofloxacin patients did about the same. Reflecting the chronicity of CBP, some patients who did not have a particular symptom at admission developed a new symptom by posttherapy. In cases in which a new symptom developed, but symptoms present at admission resolved it was up to the clinical investigator to decide clinical outcome based on his knowledge on **patient's baseline symptoms and clinical judgement.**

Poststudy assessment of microbiologic relapse by patients' infections

All patients who were cured or improved at the post-therapy visit and who had a poststudy evaluation are included in this table.

Microbiologic Response Rates by Patient's Infection at Poststudy in MBE Population

Response	Levofloxacin (N=102)	Ciprofloxacin (N=91)
	n (%)	n (%)
Long-Term Eradication*	63 (61.8)	68 (74.7)
Relapse	15 (14.7)	9 (9.9)
Persisted#	16 (15.7)	7 (7.7)
Unknown	8 (7.8)	7 (7.7)

* includes presumed eradicated
# includes presumed persisted
Adapted from Table 15 of CAPSS-101 Study Report

MO Comment: Of the 193 subjects, who were eligible for poststudy evaluation, only 31 had cultures taken at poststudy. Most patients had their microbiologic status inferred at poststudy based on clinical evaluation. More relapses and persistences were seen in the levofloxacin arm.

Poststudy Clinical Success

Clinical Response at Poststudy Visit		
	Levofloxacin n/N (%)	Ciprofloxacin n/N (%)
Long-Term Success	68/102 (66.7)	70/91 (76.9)
Clinical Relapse	26/102 (25.5)	13/91 (14.3)
Unable to Evaluate	8/102 (7.8)	8/91 (8.8)

Adapted from Table 23 of CAPSS-101 Study Report

MO Comment: A total of 94/102 levofloxacin patients who were eligible for assessment at poststudy were clinically evaluated, compared to 83/91 patients in the ciprofloxacin arm. Clinical success was 66.7% for the levofloxacin arm compared to 76.9% in the ciprofloxacin arm, indicating that the long-term success for levofloxacin was lower than that of ciprofloxacin at poststudy (95% CI [-23.40, 2.89]).

Poststudy assessment of microbiologic relapse by pathogen

Microbiologic Response by Pathogen Poststudy in MBE Population		
E.coli	Levofloxacin	Ciprofloxacin
Eradicated	2/14 (14.3)	0
Presumed Eradicated	7/14 (50.0)	6/7 (85.7)
Presumed Relapse	4/14 (28.6)	0
Unknown	1/14 (7.1)	1/7 (14.3)
E.faecalis		
Eradicated	6/41 (14.6)	5/32 (15.6)
Presumed Eradicated	18/41 (43.9)	20/32 (62.5)
Relapse	2/41 (4.9)	0
Presumed Relapse	2/41 (4.9)	2/32 (6.3)
Persisted	1/41 (2.4)	0
Presumed Persisted	8/41 (19.5)	1/32 (3.1)
Unknown	4/41 (9.8)	4/32 (12.5)
S.epidermidis		
Eradicated	0	3/25 (12.0)
Presumed Eradicated	11/16 (68.8)	16/25 (64)
Relapse	1/16 (6.3)	0
Presumed Relapse	1/16 (6.3)	0
Persisted	0	0
Presumed Persisted	1/16 (6.3)	0
Unknown	2/16 (12.5)	1/25 (14.3)

Categories for which there were 0 pathogens in both arms were omitted from table
Adapted from Table 16 of CAPSS-101 Study Report

MO Comment: The combined eradication and presumed eradication rate at the one month follow up visit was higher for ciprofloxacin than for levofloxacin for *E.coli*, *E.faecalis*, and *S.epidermidis* (difference in eradication ciprofloxacin-levofloxacin 21.4%, 19.6% and 7.2% respectively). The explanation for this finding is unclear at this time.

Other Sub-Analysis

Patients without prostate tenderness

Efficacy Results by Presence or Absence of Prostate Tenderness at Admission Visit in the MBE Population

	Levofloxacin	Ciprofloxacin
Microbiologic Response Rate		
Prostate tenderness	87/117 (74.4%)	79/106 (74.5%)
No prostate tenderness	15/19 (79.0%)	17/19 (89.5%)
Clinical Cure Rate		
Prostate tenderness	32/117 (27.4%)	30/106 (28.3%)
No prostate tenderness	8/19 (42.1%)	8/19 (42.1%)
Clinical Success Rate		
Prostate tenderness	87/117 (74.4%)	76/106 (71.7%)
No prostate tenderness	15/19 (79.0%)	15/19 (79.0%)

Adapted from Table 9 of Dr. Kathleen Fritsch's Statistical Review

MO Comment: Microbiologic response rate was comparable between the two study arms for patients with tenderness. The levofloxacin patients without tenderness had a lower microbiologic response rate than the ciprofloxacin patients (79.0% vs. 89.5%). Clinical cure rates were similar but higher for patients without prostate tenderness than those with tenderness. This difference is not as apparent in the clinical success rate. Similar findings were **seen in the MITT population, for details see Dr.Fritsch's review.** Because sample sizes were small it is difficult to draw conclusions from these differences. An analysis of the type of organisms isolated in the patients without tenderness was undertaken. Four patients had persistence in the levofloxacin arm and no pattern was found among the organisms these included: *S. agalactiae*; *S.epidermidis*; *S.haemolyticus*, *S.simulans*, *S.mitis* (all in one patient); *C.diversus*, S coagulase-negative and *E.faecalis* (all in one patient). Two patients had persistence in the ciprofloxacin arm one with *S.epidermidis* and *S.agalactiae*. The most common organism eradicated among patients without tenderness in both arms of the study was *E. faecalis*.

Center effect

A total of 65 centers enrolled patients for CAPSS-101. Of these 9 centers enrolled 10 or more patients in the MITT population, this includes Center 7 which enrolled 40 patients in the MITT population. Dr. Kathleen Fritsch performed an analysis pooling the results of the 56 remaining centers against the 9 high-enrolling centers. None of the large centers appears to have results that are unusual when compared to other centers in terms of microbiological eradication or clinical cure **rates. For more details please see Dr. Fritsch's review.**

In vitro Susceptibilities of Pathogens to Study Drugs

In Vitro Susceptibility of Admission Pathogens in MBE Population

	Levofloxacin	Ciprofloxacin
	n (%)	n (%)
Susceptible	192 (91.9)	160 (85.1)
Intermediate	9 (4.3)	5 (2.7)
Resistant	8 (3.8)	23*[22] (12.2)
Unknown	4	5
Total	213	193

*Analysis of datasets by MO yielded a discrepancy with 22 resistant isolates in the ciprofloxacin arm. Reviewing team used culture data from central lab to create list of resistant pathogens. Applicant used data from central and local labs.

Adapted from Table 10 of CAPSS-101 Study Report

MO Comment: Although on admission similar numbers of resistant pathogens were granted protocol violation waivers, subjects subsequently found to have a resistant pathogen could remain in the trial if they were improved during assessment at visit 3. Because the trial was blinded, the effect of bias on the decision of who should remain in the trial should be minimized.

Resistant Pathogens by Study Population per MO

	Levofloxacin	Ciprofloxacin
MITT		
Pathogens	10	24
Patients with resistant pathogens	9	19
MBE		
Pathogens	8	22
Patients with resistant pathogens	7	17

MO Comment: Microbiologic eradication rates of resistant pathogens were similar in each arm of the study in both the MITT and MBE populations. However the number of clinical failures at posttherapy was greater in the ciprofloxacin arm of the study in both populations. The most common resistant pathogens isolated in the levofloxacin arm were *S.epidermidis* (3/10) and *S.haemolyticus* (3/10); and *S.epidermidis* (7/24), *S.faecalis* (5/24), and *S.haemolyticus* (4/24) in the ciprofloxacin arm. An analysis of efficacy outcomes was performed excluding patients with resistant pathogens to see if the greater number of resistant pathogens in the ciprofloxacin arm had an effect in the overall results; please see table below.

Efficacy Outcomes with and without resistant organisms per MO

	Levofloxacin n/N (%)	Ciprofloxacin n/N (%)	95% CI
Microbiologic Eradication			
MITT	119/170 (70.0)	109/151 (72.2)	(-12.44, 8.07)
MITT (- resistant)	114/161 (70.8)	98/132 (74.2)	(-14.06, 7.19)
Resistant	5/9	11/19	
MBE	102/136 (75.0)	96/125 (76.8)	(-12.58, 8.98)
MBE (-resistant)	98/129 (75.9)	86/108 (79.6)	(-14.71, 7.39)
Resistant	4/7	10/17	
Clinical Cure			
MITT	47/170 (27.6)	42/151 (27.8)	(-10.31, 9.98)
MITT (- resistant)	45/161 (27.9)	37/132 (28.0)	(-10.79, 10.63)
Resistant	2/9	5/19	
MBE	40/136 (29.4)	38/125 (30.4)	(-12.51, 10.53)
MBE (-resistant)	38/129 (29.4)	33/108 (30.5)	(-13.28, 11.08)
Resistant	2/7	5/17	
Clinical Success*			
MITT	122/170 (71.8)	107/151 (70.9)	(-9.34, 11.15)
MITT (- resistant)	114/161 (70.8)	94/132 (71.2)	(-11.22, 10.41)
Resistant	8/9	13/19	
MBE	102/136 (75.0)	91/125 (72.8)	(-13.27, 8.87)
MBE (-resistant)	95/129 (73.6)	79/108 (73.1)	(-11.27, 12.26)
Resistant	7/7	12/17	

* Clinical Success (includes cure + improvement)
(-resistant) Population with patients with resistant organisms subtracted out

MO Comment: If the patients with resistant pathogens are removed from the analysis, the microbiologic eradication rate in the MBE population is 75.9% for the levofloxacin arm compared to 79.6% in the ciprofloxacin arm (95% CI [-14.71, 7.39]). Because of the small number of patients involved, their exclusion did not impact the results of the trial. Even with the subtraction of these patients, the pre-specified delta of 20% for this outcome is met. The clinical outcomes of cure and success are similar with the inclusion or exclusion of these patients from analysis.

Superinfections

A superinfecting organism was one isolated while on-therapy through and including the posttherapy visit from cultures of any site that was associated with emergence or worsening of clinical signs and/or laboratory evidence of active infection requiring antimicrobial therapy. Nine levofloxacin treated patients developed 13 superinfections, with 11 ciprofloxacin treated patients developing 14 superinfections in the ITT population. The most common superinfecting organism was *S.haemolyticus* with 5 isolates in the ciprofloxacin arm and one in the levofloxacin arm. The most common isolates in the levofloxacin arm

were *S.epidermidis* (2) and *E.faecalis* (2). In the levofloxacin treatment group 4/13 pathogens were resistant to levofloxacin, in comparison in the ciprofloxacin treatment group 9/14 pathogens were resistant to ciprofloxacin.

MO Comment: A similar number of superinfections were seen in both study arms. A greater number of resistant superinfecting pathogens were seen in the ciprofloxacin arm of the study. It is unclear what is the clinical significance of this finding.

New Infections and Reinfections

A new infector was a pathogen not present at admission, isolated between posttherapy and poststudy, that was associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection requiring antibacterial therapy. Five new infectors (four patients) were isolated in the levofloxacin arm and three new infectors (three patients) were isolated in the ciprofloxacin arm. A reinfector was the re-emergence of the original organism isolated at admission in a patient with documented or presumed eradication at the posttherapy visit. Re-infecting organisms were obtained after posttherapy and had to be associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection requiring antibacterial therapy. Six reinfectors were found in the levofloxacin arm, and only one was found in the ciprofloxacin arm. In the levofloxacin arm 2/11 pathogens were resistant, and 1/4 were resistant in the ciprofloxacin arm. These organisms were found among the 31 cultures done at posttherapy.

MO Comment: Only 19/94 patients were cultured in the levofloxacin arm compared to 12/83 in the ciprofloxacin arm. The decision to culture rested with the clinical investigator who was blinded to treatment arm. Six reinfectors were isolated in the levofloxacin arm compared to one in the ciprofloxacin arm. An analysis of the patients with reinfectors did not elicit any possible associated factors with reinfection. No pattern was found among the type of organisms, age, or susceptibility pattern. Course of therapy was appropriate in these patients and ranged from 28-32 days. The weight of the patients with reinfectors was slightly higher than the average weight observed in this trial, however after discussion with the review **team's biopharmacologist, Dr. Phil Colangelo, this difference was felt** to be of no significance with respect to the bioavailability of levofloxacin to the site of infection. A greater number of reinfectors were seen in the levofloxacin arm and this together with clinical outcomes at poststudy suggests a trend towards better outcomes with ciprofloxacin in the long-term follow-up.

6.3. Conclusions Regarding Efficacy Data in CAPSS-101

CAPSS-101 is a randomized, controlled study showing the efficacy of a 28-day regimen of LEVAQUIN® for the treatment of chronic bacterial prostatitis. The study enrolled appropriate and relevant populations and is the basis for the approval of LEVAQUIN® for the treatment of CBP. Although the applicant submitted only one study, LEVAQUIN® is approved for the treatment of complicated urinary tract infection and may be considered for approval on the basis of one well-conducted study. The applicant met the primary efficacy result of microbiologic eradication in the MBE population at the posttherapy visit with 75% (102/136) eradication in the levofloxacin arm **and 76.8% (96/125) eradication in the ciprofloxacin arm. The 95% CI was –** 12.58, 8.98 within the pre-specified delta of 20%. Secondary endpoints at the posttherapy visit (5-18 days after completion of therapy) corroborate the efficacy of LEVAQUIN® in the treatment of chronic bacterial prostatitis. Secondary endpoints at the poststudy visit (24-45 days after completion of therapy) such as long-term eradication and clinical success were better for ciprofloxacin. Clinical success was 66.7% for the levofloxacin arm 76.9% in the ciprofloxacin arm, indicating that the long-term success for ciprofloxacin was higher than that of levofloxacin at poststudy (95% CI [-23.40, 2.89]). However, the primary efficacy endpoint was met, and the Applicant showed that at the end of therapy levofloxacin was not inferior to ciprofloxacin. This difference in outcomes at the poststudy visit will be addressed in labeling.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

Levofloxacin is as safe as ciprofloxacin for the treatment of CBP. One death was found in this study which was not attributable to study drug. No other serious adverse events were documented in CAPSS-101 in the levofloxacin treatment group. A total of 5.6% (11/197) of patients had a significant adverse event which led to drug discontinuation. The most common AEs were abdominal pain, diarrhea and dyspepsia.

7.2. Materials Utilized in the Review

- Electronic NDA 20-634 and NDA 20-635 folders
- **Applicant's Postmarketing Data submitted with this NDA**

7.3. Description of Patient Exposure

LEVAQUIN® 500mg q.d. was used for 28 days in this study. For safety evaluable patients, the median duration of levofloxacin treatment was 28 days with a mean duration of therapy of 26.6 days (range of 1-44 days). The

median duration of ciprofloxacin treatment was 28 days with a mean duration of therapy of 26.1 days (range of 1-40 days). For more detailed information on regimen compliance during the trial see section 6.2.

7.4. Safety Findings from CAPSS-101

A patient was included in the safety summaries if he received at least one dose of study drug and safety information was available. The safety evaluable population included 197 patients in the levofloxacin treatment group and 180 patients in the ciprofloxacin treatment group. Please refer to **Appendix 6 for Applicant's safety definitions.**

- **Deaths**

  One patient in the levofloxacin treatment group died during the study. Patient 51903 suffered a brain stem hemorrhage that was assessed by the investigator as not related to study drug.

  Narrative Patient 51903: Patient is a 71 year-old Caucasian male with past medical history of hypertension, basal cell carcinoma, benign prostatic hypertrophy with transurethral resection of the prostate, colon resection for colon cancer and chronic prostatitis. The patient received levofloxacin 500mg p.o. q.d. from September 19, 2000 to September 27, 2000. On [redacted] the patient presented to the hospital in respiratory failure was intubated and admitted to the ICU in a coma. He was diagnosed with a hemorrhagic brain stem infarction. He was treated with the following i.v. medications: valium, fluids, levofloxacin and decadron. He was removed from life support and expired on [redacted] The investigator considered this event severe and not related to study medication. There were no concomitant medications being taken by the patient at the time of the event.

  MO Comment: This event occurred 16 days after the last dose of levofloxacin. The investigator did not feel that this event was related to the **study drug and MO's assessment after review of the information available** for this subject and CRF is consistent with that of the investigator.

- **Other Serious Adverse Events (AE)**

  All serious AEs documented in this trial were felt not to be related to study drug. In the levofloxacin arm one death was documented for details see previous section.
  One patient (25903) in the ciprofloxacin arm experienced two serious AEs: depression and increased anxiety both of marked severity.

  Narrative Patient 25903: Patient is a 54 year-old Caucasian male with a

past medical history of anxiety/panic disorder, sinus disease, hypertension, irritable bowel syndrome, bilateral carpal tunnel syndrome, spondylitis, hemorrhoidectomy and chronic prostatitis. This patient received ciprofloxacin 500mg p.o. b.i.d. from March 13, 2001 to April 9, 2001. On March 29, 2001, the patient experienced increased anxiety related to a family illness. His medication was changed from alprazolam to gabapentin to citalopram on April 3, 2001. He was hospitalized in a psychiatric facility on [redacted] The investigator considered this a severe event not related to study medication. Concomitant medications included lisinopril, ranitidine, rabeprazole, alprazolam, psyllium, phenazopyridine, acetominaphen, diphenhydramine, citalopram, gabapentin, parecetamol, buspirone, saw palmetto and echinacea.

MO Comment: This event was felt to not be related to study drug by the investigator. This patient had a preceding psychiatric history and a possible stressor prior to AE.

- **Other Significant Adverse Events**

  Adverse events which led to discontinuation of therapy were found in 11/197 (5.6%) in the levofloxacin arm and 8/180 (4.4%) in the ciprofloxacin arm. Events which were found in more than one patient were abdominal pain, diarrhea and dyspepsia in the levofloxacin arm and nausea in the ciprofloxacin arm. Please see Appendix 5 for details.

MO Comment: A comparable number of patients discontinued therapy in the safety evaluable population in each study arm.

- **All Adverse Events**

  One treatment-emergent AE was experienced by 87/197 (44.2%) in the levofloxacin arm and 67/180 (37.2%) in the ciprofloxacin arm. The body system with the highest reported frequency of AEs was the gastrointestinal system with a rate of 18.8% in the levofloxacin group and 17.2% in the ciprofloxacin group.

Incidence of Treatment Emergent AEs by Body System in the Safety Evaluable Population

	Levofloxacin N=197	Ciprofloxacin N=180
Gastrointestinal	37 (18.8)	31 (17.2)
Musculoskeletal	19 (9.6)	15 (8.3)
Body as a Whole	18 (9.1)	15 (8.3)
Nervous System	17 (8.6)	19 (10.6)
Respiratory	16 (8.1)	15 (8.3)
Skin and Appendages	13 (6.6)	11 (6.1)
Psychiatric	6 (3.0)	7 (3.9)
Cardiovascular	4 (2.0)	2 (1.1)
Urinary	3 (1.5)	3 (1.7)
Vascular	2 (1.0)	0
Vision	1 (0.5)	0
Metabolic/Nutritional	1 (0.5)	2 (1.1)
Heart Rate/Rhythm	1 (0.5)	0
White Cell and RES	1 (0.5)	1 (0.6)
Platelet, Bleeding/Clotting	1 (0.5)	1 (0.6)
Reproductive, Male	1 (0.5)	2 (1.1)
Application Site	1 (0.5)	0
Resistance	1 (0.5)	3
Special Senses	0	1 (0.6)
Neoplasm	0	1 (0.6)
Total*	87 (44.2)	67 (37.2)

*** 95% CI – 3.23, 17.12**
RES reticuloendothelial system
Adapted from Table 32 of CAPSS-101 Study Report

MO Comment: The number of treatment emergent adverse events is comparable in both study arms. The most common AEs reported in the levofloxacin arm were gastrointestinal and musculoskeletal disorders, and gastrointestinal and nervous system disorders in the ciprofloxacin arm.

Incidence of Frequently* Reported AEs Primary Terms		
	Levofloxacin (N=197)	Ciprofloxacin (N=180)
All Body Systems	87 (44.2)	67 (37.2)
Body as a Whole-General		
Back Pain	3 (1.5)	5 (2.8)
Nervous System		
Headache	12 (6.1)	12 (6.7)
Dizziness	1 (0.5)	7 (3.9)
Gastrointestinal		
Nausea	11 (5.6)	9 (5.0)
Abdominal Pain	10 (5.1)	6 (3.3)
Diarrhea	8 (4.1)	6 (3.3)
Constipation	6 (3.0)	4 (2.2)
Dyspepsia	4 (2.0)	7 (3.9)
Flatulence	1 (0.5)	4 (2.2)
Musculoskeletal		
Arthralgia	8 (4.1)	5 (2.8)
Myalgia	7 (3.6)	6 (3.3)
Skeletal Pain	3 (1.5)	5 (2.8)
Respiratory System		
Rhinitis	5 (2.5)	5 (2.8)
URI	5 (2.5)	4 (2.2)
Skin and Appendages		
Rash	2 (1.0)	5 (2.8)

* Reported by ≥2.0% of patients in either treatment group
URI upper respiratory tract infection

MO Comment: Side effects, which were reported in 5% or more of the patients, were headache, nausea and abdominal pain for the levofloxacin arm and headache and nausea for the ciprofloxacin arm. More patients reported dizziness in the ciprofloxacin arm (3.9%) compared to the levofloxacin arm (0.5%). There are minor differences in the type of AEs seen but the numbers are too small to draw significant conclusions. The overall rate of AEs is similar in both arms.

Nineteen (19/197 9.6%) adverse events were felt to be probably or very likely related to study drug in the levofloxacin arm compared to ten (10/197 5.6%) in the ciprofloxacin arm. The gastrointestinal system was most commonly involved in both arms. Three AEs required treatment in the levofloxacin versus two in the ciprofloxacin arm.

The majority of AEs were mild or moderate in severity. A severe AE was identified in 15/197 patients (7.6%) in the levofloxacin arm and 7/180 (3.9%) patents in the ciprofloxacin arm. In the levofloxacin arm the most common AEs of marked severity were abdominal pain and constipation. In the ciprofloxacin arm the most common AE of marked severity was headache. Fifteen patients in the levofloxacin arm reported 21 severe AEs, of these 9 were considered related to levofloxacin. Similarly 7 patients reported 12

severe AEs of these 1 was felt to be related to ciprofloxacin.

- QT prolongation
  No EKG monitoring was performed in this study. However, no changes in heart rate were observed between admission and posttherapy.

MO Comment: An analysis of AEs in the safety database of CAPSS-101 was undertaken by MO to verify that other AEs which could be attributed to QT prolongation were not missed. These included fainting, syncope, fall, dizziness, light headedness, vertigo, and palpitations. One instance of vertigo was found in the levofloxacin arm and 8 instances of dizziness or light headedness were observed in the ciprofloxacin arm. No concerning trends were observed.

- Laboratory Findings
  There were no clinically relevant mean changes from admission to posttherapy for any laboratory analyte in either treatment group.
  For details please see Appendix 7.

  Individual Clinically Significant Abnormalities
  Seven (7/197 3.6%) of the levofloxacin patients and seven (7/180 3.9%) of the ciprofloxacin patients had treatment-emergent markedly abnormal clinical laboratory values. Four patients in the levofloxacin arm had low glucose levels which was the most common abnormal finding in this group, likewise three patients had decreased neutrophils the most common abnormal finding in the ciprofloxacin group. No patient in either group had treatment-emergent markedly abnormal clinical laboratory values that were reported as serious adverse events, adverse events that led to discontinuation of therapy, or adverse events of marked severity.

- Vital Signs

Mean Values and Mean Changes in Vital Signs*

	Levofloxacin			Ciprofloxacin		
	N	Mean Admission ±SD	Mean Change ±SD	N	Mean Admission ±SD	Mean Change ±SD
Oral temperature (°C)	174	36.6± 0.49	-0.0 ± 0.58	160	3.6±0.50	-0.1±0.52
Respiratory Rate (beats/minute)	179	16.4± 2.85	0.20±2.72	164	16.6±2.80	0.2±2.61
Heart Rate (beats/minute)	179	71.3±9.99	0.2±9.41	165	72.5±9.83	-0.2±9.66
Systolic blood pressure (mm/Hg)	179	130.0±16.81	-2.6±13.31	164	129.1±15.02	-0.9±13.72
Diastolic blood pressure (mm/Hg)	179	80.4±9.88	-0.7±9.00	164	80.3±9.23	-0.2±9.49

* Changes between Admission and Posttherapy
Systolic and Diastolic blood pressure in mm/Hg

MO Comment: The observed mean changes in vital signs were small and similar in the two treatment groups. There were no clinically significant mean changes in either treatment group.

7.5. Miscellaneous Studies

No miscellaneous studies were submitted with this application.

7.6. Literature Review for Safety

The Applicant provided three references for their literature review of safety discussed below.

In Kawada et al[14] levofloxacin was administered to 539 patients 56 of which had prostatitis. The other patients had a variety of genitourinary infections. The daily dose ranged from 100-600mg from 3-14 days. The rate of AE was 2.8% out 530 patients. 18 events were reported by 15 patients and required therapy discontinuation in 6/15 patients. Half of the events reported were gastrointestinal disorders. Severe AEs were reported in 5/18 patients. The incidence of abnormal laboratory findings was 5.6% in 322 patients; the most common abnormal change was liver function tests noted in 14 events. None of these changes were considered clinically significant.

MO Comment: This study had lower rate of total AEs than was observed in CAPSS-101. The most common AE seen in this study was gastrointestinal as was seen in CAPSS-101. It is difficult to draw conclusions from this uncontrolled study with a shorter duration of therapy than was used in CAPSS-101.

Two other Japanese studies (Suzuki and Horiba[15] and Matsui et al[16]) examined the effect of levofloxacin in prostatitis. A total of 48 patients with prostatitis and 6 with other genitourinary infections received levofloxacin for 7-14 days. One patient experienced anorexia and dizziness which resolved off drug, and three patients had mild elevations in liver function tests which were deemed not clinically significant. One patient had thrombocytopenia and elevated BUN.

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[14] Kawada Y, Kazuhisa O, Shino M, et al. Usefulness of levofloxacin in genitourinary tract infection. Genitourinary Tract Infections/Levofloxacin. May 1992; (40 S-3):249-266.
[15] Suzuki K, Horiba M. Clinical study of levofloxacin (DR-3355) on uro-genital infections. Acta Urol. 1992; Jpn. 38:737-743.
[16] Matsui T, Lee M, Sakai Y, et al. Clinical effects of levofloxacin on prostatitis, and fluctuations of cytokines in urinary or expressed prostatic secretion. J Japan Society of Chemotherapy. February 1999; (47):89-96.

MO Comment: Three patients had mild elevation in liver function tests in these Japanese studies. One patient had markedly abnormal liver function tests in the levofloxacin treatment group with a change in bilirubin from 1.3 to 2.7mg/dL 28 days after last levofloxacin dose. This event was not felt to be a serious AE by the author. In comparison, there was no significant mean change from admission to posttherapy in liver function tests in CAPSS-101.

MO Comment: Ovid Search by MO of the medical literature using the following search terms: anti-infective agents, fluoroquinolone/adverse effects limited to human and articles with abstracts and further limited to medical publications alone yielded 16 citations. A second search was performed using the terms prostatitis and adverse events which yielded 10 citations. These were limited to relevant articles which are discussed below.

In a study of CBP (N=112) using a treatment regimen of 28-days AEs involving the digestive and nervous system were observed most frequently[17]. An open-label study which enrolled 27 patients with CBP for treatment with 28-days of rufloxacin with follow-up to one month after completion of therapy, identified one AE which was felt to be related to drug and involved the central nervous system[18]. Treatment of latent multidrug-resistant tuberculosis with pyrazinamide and levofloxacin was evaluated using a case series of 17 patients. Fourteen patients in this case series developed musculoskeletal adverse events, of which 11 were felt to be probably related to drug therapy. Eight patients reported central nervous system effects and five instances of hepatocellular injury were reported[19].

[17] Cox CE and Childs SJ. Treatment of chronic bacterial prostatits with temafloxacin. Am J Med. 1991;91(6A):134S-9.

[18] Boerema JB et al. An open multicentre study on the efficacy and safety of rufloxacin in patients with chronic bacterial prostatitis. Journal of Antimicrobial Chemotherapy. 1991; 28(4):587-97.

[19] Papastavros T et al. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multi-drug resistant tuberculosis. Canadian Medical Assoc Journal. 2002;167(2)131-6.

MO Comment: These studies were small and did not identify any unique and unrecognized adverse event. The study in which combination therapy with pyrazinamide and levofloxacin was evaluated is difficult to interpret because it is a case-series without a comparator with a small number of patients. Side effects observed were high but difficult to ascertain to either drug.

7.7. Postmarketing Surveillance

There have been an estimated 43 million patient exposures for levofloxacin in the U.S. from 1996-2002. There were a total of 8,561 spontaneous adverse reactions. In the US, the most commonly reported serious adverse reactions by body system were musculoskeletal, body as a whole, nervous, gastrointestinal and psychiatric system.

There were 1379 musculoskeletal adverse reactions regardless of seriousness, the most frequent diagnosis was arthralgia, tendon disorder, myalgia, tendonitis. Tendon rupture was reported 174 times in the US and 303 times abroad.

7.8. Safety Update

Since the last safety update filed in December 2001, the levofloxacin clinical safety database has been expanded to incorporate CAPSS-101. This database with a total of 8,615 patients evaluable for safety of which 5,151 were treated with levofloxacin. This data comes from 23 Phase 3 Studies including CAPSS-101.

For active controlled Phase 3 trials, 41.1% (1429/3480) of the levofloxacin-treated patients reported a treatment-emergent adverse event regardless of relationship to drug, compared to 43.1% (1494/3464) in the control drug-treated patients. The 95% confidence interval for the between-group difference was [-0.3, 4.4].

MO Comment: Of note is that the average length of treatment for studies in which levofloxacin was administered orally was 10.4±6.19, and 11.4±8.33 days in which it was administered orally and i.v. These averages include CAPSS-101 in which the mean number of days of therapy was 26.6±6.57.

The body systems with the highest incidence of AEs in the levofloxacin-treated patients were the gastrointestinal system 18.4%, the nervous system 9.2% and the body as a whole 8.7%. Adverse events occurring in ≥2% of levofloxacin treated patients were nausea, diarrhea, abdominal pain and constipation, dyspepsia, vomiting, headache, dizziness and insomnia. Most adverse events were mild or moderate in severity. Fifteen percent of adverse events reported in the levofloxacin-treatment group were of marked severity (220/1429).

Treatment-Emergent Adverse Events by Dose of Levofloxacin in Safety Evaluable Population

Dose	AE rate n/N (%)
CAPSS-101 500mg q.d.	87/197 (44.2)
All other 250/500mg q.d.	1,739/4,162 (41.8)
All 250/500mg q.d.	1,826/4,359 (41.9)
All 750mg q.d.	267/439 (60.8)
All Phase 3 studies	2,241/5,151 (43.5)

Adapted from Applicant's Integrated Summary of Safety- Attachment 2.5
The 750mg studies include nosocomial pneumoniae and complicated skin and skin structure infection studies

MO Comment: If adverse event rates are compared based on levofloxacin dose, similar rates of total AEs are seen except for the 750mg q.d. dose which had a higher rate of AEs.

The proportion of patients who discontinued study medication due to a **treatment-emergent AE remains unchanged from the Applicant's last safety** update. In active controlled studies 4.0% levofloxacin-treated and 3.8% control-drug treated patients discontinued therapy.

MO Comment: In CAPSS-101 a similar number of patients discontinued therapy due to an AE, 5.6% of the levofloxacin-treated patients compared to 4.4% in the ciprofloxacin-treated patients.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

Section below from LEVAQUIN® current label

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.

7.10. Adequacy of Safety Testing

A total of 377 patients were enrolled in the safety evaluable populations, 197 in the levofloxacin-treatment arm and 180 in the ciprofloxacin arm. The number of treatment-emergent AEs observed in CAPSS-101 is similar to the rate of AEs observed in other Phase 3 trials, except for the nosocomial pneumoniae trial, which had a higher rate of AEs. No clinically relevant changes in laboratory parameters were observed, no deaths attributable to drug occurred in the levofloxacin-treatment group. A similar number of patients discontinued medication due to an AE in the levofloxacin arm vs. the ciprofloxacin arm (5.6%, 4.4% respectively).

7.11. Labeling Safety Issues and Postmarketing Commitments

No safety issues were identified in the safety review that warrant postmarketing commitments. Adverse events observed in this trial are consistent with those seen in prior studies.

8. Dosing, Regimen, and Administration Issues

LEVAQUIN®'s **proposed dosing regimen for the treatment of CBP is 500mg** p.o. q.d. for 28 days. This is the same dose and frequency used for LEVAQUIN®'s **other approved indications: acute bacterial exacerbation of** chronic bronchitis, community-acquired pneumoniae, acute maxillary sinusitis, and uncomplicated skin and skin structure infection. A higher dose, 750mg, has been approved for the treatment of complicated skin and skin structure infection. The length of therapy for these other indications ranges from 7-14 days. This would be the first indication granted for an extended period of therapy of 28 days. The safety profile of CAPSS-101 was in line with other Phase 3 studies.

9. Use in Special Populations

Gender

CBP is a condition found only in males and only male patients were recruited into CAPSS-101.

The levofloxacin treated male patients in CAPSS-101 differed in that they had a higher incidence of arthralgia and myalgia (4.1%, 3.6% respectively) than was seen in other Phase 3 studies (0.5%, 0.4%). Similarly, the ciprofloxacin-treated male patients in CAPSS-101 experienced a higher incidence of arthralgia and myalgia (2.8% vs. 3.3% respectively). Applicant analysis found no relationship between duration of therapy and either occurrence or frequency of these AEs.

Race

- Efficacy

Efficacy Results at Posttherapy by Race

	MBE		MITT	
	Levofloxacin	Ciprofloxacin	Levofloxacin	Ciprofloxacin
Microbiological Response Rate				
Caucasian	71/97 (73.2%)	70/90 (77.8%)	84/125 (67.2%)	79/110 (71.8%)
Black	17/20 (85.0%)	13/19 (68.4%)	18/21 (85.7%)	15/22 (68.2%)
Asian	1/1 (100%)	2/2 (100%)	2/3 (66.7%)	2/2 (100%)
Other	13/18 (72.2%)	11/14 (78.6%)	15/21 (71.4%)	13/17 (76.5%)
Clinical Cure Rate				
Caucasian	27/97 (27.8%)	28/90 (31.1%)	31/125 (24.8%)	31/110 (28.2%)
Black	7/20 (35.0%)	6/19 (31.6%)	8/21 (38.1%)	6/22 (27.3%)
Asian	0/1 (0%)	1/2 (50.0%)	1/3 (33.3%)	1/2 (50.0%)
Other	6/18 (33.3%)	3/14 (21.4%)	7/21 (33.3%)	4/17 (23.5%)
Clinical Success Rate				
Caucasian	71/97 (73.2%)	65/90 (72.2%)	85/125 (68.0%)	79/110 (71.8%)
Black	17/20 (85.0%)	16/19 (84.2%)	18/21 (85.7%)	16/22 (72.7%)
Asian	1/1 (100%)	2/2 (100%)	3/3 (100%)	2/2 (100%)
Other	13/18 (72.2%)	8/14 (57.1%)	16/21 (76.2%)	10/17 (58.8%)

From Dr. Kathleen Fritsch Statistical Review

MO Comment: The majority of the patients in CAPSS-101 were Caucasian. Twenty-one Black patients were included in the levofloxacin arm compared to 22 in the ciprofloxacin arm in the MITT population. No difference in efficacy outcome at the posttherapy visit was found between Black and Caucasian patients. Too small a number of Asian patients were included to draw any meaningful conclusions.

- Safety

Treatment-Emergent AEs by Race CAPSS-101 vs. Other Phase 3 Studies

	Levofloxacin		Control Drug	
Race	CAPSS-101	Phase 3 Studies	CAPSS-101	Phase 3 Studies
Caucasian	72/146 (49.3)	1623/3521 (46.1)	51/134 (38.1)	1026/2259 (45.4)
Black	6/24 (25.0)	348/965 (36.1)	9/24 (37.5)	280/666 (42.0)
Other	9/27 (33.3)	183/468 (39.1)	7/22 (31.8)	121/359 (33.7)

Adapted from Applicant's Integrated Summary of Safety Attachment 4.17.1-4.17.3

MO Comment: Fewer adverse events were observed among Black and other subjects in CAPSS-101. This trend was also seen in other Phase 3 studies in which 36.1% of all black subjects experienced an AE vs. 46.1% of all Caucasian patients. This lower incidence of AEs in Black and other subjects was not observed in the control drug arm.

Age

- Efficacy

Efficacy Results at Posttherapy by Age Group

	MBE		MITT	
	Levofloxacin	Ciprofloxacin	Levofloxacin	Ciprofloxacin
Microbiological Response Rate				
≤ 45	31/44 (70.5%)	35/44 (79.6%)	39/58 (67.2%)	38/52 (73.1%)
46-64	54/69 (78.3%)	44/57 (77.2%)	61/85 (71.8%)	52/70 (74.3%)
≥ 65	17/23 (73.9%)	17/24 (70.8%)	19/27 (70.4%)	19/29 (65.5%)
Clinical Cure Rate				
≤ 45	9/44 (20.5%)	12/44 (27.8%)	12/58 (20.7%)	13/52 (25.0%)
46-64	21/69 (30.4%)	15/57 (26.3%)	24/85 (28.2%)	17/70 (24.3%)
≥ 65	10/23 (43.5%)	11/24 (45.8%)	11/27 (40.7%)	12/29 (41.4%)
Clinical Success Rate				
≤ 45	31/44 (70.5%)	29/44 (65.9%)	40/58 (69.0%)	35/53 (67.3%)
46-64	53/69 (76.8%)	44/57 (77.2%)	61/85 (71.8%)	51/70 (72.9%)
≥ 65	18/23 (78.3%)	18/24 (75.0%)	21/27 (77.8%)	21/29 (72.4%)

From Dr. Kathleen Fritsch Statistical Review

MO Comment: Microbiologic response rate is similar among different age groups. Clinical cure rates are higher among patients ≥65 years both in the MBE and in the MITT population. This trend is not as clear in the clinical success rate, which is more homogenous among age groups.

- Safety
  In CAPSS-101, the incidence of treatment-emergent adverse events for patients <65 and ≥65 years in the levofloxacin-treatment group was 44.4% and 42.9%. The incidence of AE was comparable between elderly and younger patients in the other 250/500mg q.d. studies and in the 750mg q.d. levofloxacin studies.

9.1. Pediatric Program

Text below from Applicant's CAPSS-101 submission

As necessary studies are impossible or highly impractical due to the fact that chronic bacterial prostatitis is not a disease state occurring in the pediatric population, J&JPRD hereby requests a full waiver for pediatric studies for this indication.

MO Comment: A waiver for pediatric studies for CBP is appropriate.

9.2. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

Renal

Levofloxacin dosage adjustments are needed to avoid its accumulation due to decreased renal clearance.

Hepatic

Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. However, the condition of CBP is only found in males and therefore is not relevant to pregnancy.

10. Conclusions, Recommendations, and Labeling

10.1. Conclusions Regarding Safety and Efficacy

Levofloxacin was well tolerated and was as effective as ciprofloxacin in the treatment of chronic bacterial prostatitis. This product, which is a once daily formulation, will add to the armamentarium of available regimens for CBP. No serious risks were identified in this study. The most common side effects were disorders of the gastrointestinal system.

10.2. Recommendations on Approvability.

From a clinical perspective levofloxacin is approved for the treatment of chronic bacterial prostatitis associated with the following pathogens: *E.coli*, *Enterococcus faecalis* and *Staphylococcus epidermidis*.

10.3. Labeling

Only the portions of the label addressing the CBP indication will be addressed in this review.

The Applicant's proposed labeling for CBP is:

INDICATIONS AND USAGE

Chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, [redacted]

DOSAGE AND ADMINISTRATION

Patients with Normal Renal Function

Infection	Unit Dose	Frequency	Duration	Daily Dose
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg

CLINICAL STUDIES

Chronic Bacterial Prostatitis

Pathogen	Levofloxacin (N=136)		Ciprofloxacin (N=125)	
	N	Eradication	N	Eradication
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	45	34 (75.6%)
S. epidermidis	24	20 (83.3%)	29	26 (89.7%)

Clinical success rates in the microbiologically evaluable population were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin patients (95% CI [-13.27, 8.87]) indicating that once daily levofloxacin was as effective as twice daily ciprofloxacin in the treatment of chronic bacterial prostatitis.

MO's Proposal for the Label

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Patients with Normal Renal Function

Infection	Unit Dose	Frequency	Duration	Daily Dose
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg

CLINICAL STUDIES

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:

Pathogen	Levofloxacin (N=136)		Ciprofloxacin (N=125)	
	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).

Appendix

1. NUMBER OF PATIENTS BY ANALYSIS POPULATION AND STUDY CENTER
2. PATIENTS EXCLUDED FROM ITT POPULATION
3. CLINICAL SIGNS AT ADMISSION OF ITT POPULATION
4. CLINICAL SYMPTOMS AT ADMISSION OF ITT POPULATION
5. TREATMENT-EMERGENT AES RESULTING IN DISCONTINUATION OF THERAPY
6. SAFETY DEFINITIONS USED BY APPLICANT
7. MEAN VALUES AND MEAN CHANGES IN CLINICAL LABORATORY RESULTS

APPENDIX 1 NUMBER OF PATIENTS BY ANALYSIS POPULATION AND STUDY CENTER

Number of Patients by Analysis Population and Study Center

	Levofloxacin					Ciprofloxacin				
Investigator	ITT	MITT	MBE	NBE	Safety	ITT	MITT	MBE	NBE	Safety
Aliotta	3	2	2	0	3	0	0	0	0	0
Apaydin	1	0	0	0	1	3	3	3	0	3
Bar-chama	2	2	2	0	2	0	0	0	0	0
Bauer	2	2	1	0	2	2	2	2	0	2
Bejany	2	1	1	0	2	1	1	1	0	1
Bernstein	2	2	1	0	2	5	3	3	1	5
Bidair	4	2	1	0	4	4	4	4	0	4
Bilhartz	2	2	1	0	2	1	1	1	0	1
Bundrick	18	15	12	1	18	16	14	14	0	16
Byrne	1	1	0	0	1	1	1	1	0	1
Canfield	0	0	0	0	0	1	1	1	0	1
Cohen	1	1	1	0	1	1	0	0	1	1
Cook	0	0	0	0	0	1	0	0	1	1
Cox	1	1	1	0	1	0	0	0	0	0
Demby	1	1	1	0	1	1	1	1	0	1
Donnell	0	0	0	0	0	3	1	1	1	3
Elist	1	0	0	1	1	2	0	0	1	2
Eppel	0	0	0	0	0	2	2	2	0	2
Esrig	2	2	2	0	2	1	1	1	0	1
Fallick	0	0	0	0	0	2	1	1	0	2
Feldman	4	4	2	0	4	3	3	3	0	3
George	0	0	0	0	0	1	1	1	0	1
Gittelman	3	2	2	0	3	3	3	1	0	3
Grable	4	2	1	2	4	0	0	0	0	0
Halpern	7	7	6	0	7	7	5	4	0	7
Harper	1	1	0	0	1	0	0	0	0	0
Heron	10	9	9	0	10	11	9	7	1	11
Horn	3	3	3	0	3	2	2	1	0	2
Hornick	3	2	2	0	3	1	0	0	0	1
Howland	6	5	5	0	6	5	5	5	0	5
Jones	2	2	1	0	2	0	0	0	0	0
Klein, T	1	1	1	0	1	0	0	0	0	0
Magura	2	2	2	0	2	1	1	1	0	1
Makovsky	0	0	0	0	0	2	1	1	0	2
Mendez	1	1	0	0	1	0	0	0	0	0
Narayan	2	1	0	0	2	2	2	1	0	2
Parr	4	4	4	0	4	4	4	3	0	4
Parramore	3	2	2	0	3	1	1	0	0	1
Pittman	7	6	3	0	7	7	5	3	1	7
Ray	21	20	17	0	21	22	20	17	0	22
Rhudy	2	2	2	0	2	2	2	2	0	2
Robinson	1	1	1	0	1	0	0	0	0	0
Rowe	1	1	1	0	1	1	1	0	0	1
Saslawsky	2	1	1	0	2	3	2	2	1	3
Scaljon	2	2	1	0	2	0	0	0	0	0
Schiff	17	17	14	0	17	15	15	13	0	15
Sharkey	7	7	5	0	7	7	7	7	0	7
Shoemaker	7	5	5	0	7	6	6	4	0	6
Sievers	1	1	1	0	1	2	1	1	0	2
Smith, C	1	1	0	0	1	1	1	0	0	1
Smith, R	2	2	2	0	2	0	0	0	0	0
Smith, S	3	3	3	0	3	2	2	1	0	2
Stallings	2	2	2	0	2	2	2	1	0	2
Steidle	0	0	0	0	0	1	1	0	0	1
Susset	1	1	1	0	1	2	2	1	0	2
Tawil	3	3	1	0	3	3	3	3	0	3
Thrasher	4	3	2	0	4	0	0	0	0	0
Turner	1	1	1	0	1	1	1	1	0	1
Uy	3	1	1	1	3	2	1	1	1	2
Wachs	3	2	1	0	3	2	1	1	0	2
Walzer	2	2	2	0	2	1	0	0	1	1
Wescott	4	4	3	0	4	5	4	3	0	5

Number of Patients by Analysis Population and Study Center

	Levofloxacin					Ciprofloxacin				
Investigator	ITT	MITT	MBE	NBE	Safety	ITT	MITT	MBE	NBE	Safety
Wilson	1	0	0	0	1	1	0	0	0	1
Young, D	0	0	0	0	0	1	1	0	0	1
Young, J	0	0	0	0	0	1	0	0	0	1
Total	197	170	136	5	197	180	151	125	10	180

[a] The following investigators randomized patients who did not receive drug; they are not included in the above counts: Hornick, Ciprofloxacin, N=1, Patient: 49904; Levin, Ciprofloxacin, N=1, Patient: 65901; Parr, Levofloxacin, N=1, Patient: 94902; Schiff, Ciprofloxacin, N=2, Patients: 46927, 46929; Schiff, Levofloxacin, N=1, Patient: 46935;

Adapted from Table 8 of CAPSS-101 Study Report

APPENDIX 2 PATIENTS EXCLUDED FROM ITT POPULATION

1903	62910
7921	62917
7925	62925
7929	66901
8903	68903
17915	70901
17920	75904
17921	75905
19904	78902
19907	84901
25901	84911
25902	84914
29905	88902
32904	88905
32907	89901
34902	89902
36901	93901
41903	101905
42903	101912
42904	104902
44902	106902
49902	106904
49905	106905
50911	108903
60912	110901
60913	110902
62901	110903
62908	114901

APPENDIX 3 CLINICAL SIGNS AT ADMISSION

Clinical Signs at Admission of Intent-to Treat Population			
	Levofloxacin (197) N (%)	Ciprofloxacin (180) N (%)	Total (377) N (%)
Fever			
N	194	179	373
None	189 (97.4)	174 (97.2)	363 (97.3)
Mild	4 (2.1)	4 (2.2)	8 (2.1)
Moderate	1 (0.5)	1 (0.6)	2 (0.5)
Severe	0	0	0
Unknown	3	0	3
Missing	0	1	1
Rigor			
N	195	175	370
None	193 (99.0)	171 (97.7)	364 (98.4)
Mild	2 (1.0)	3 (1.7)	5 (1.4)
Moderate	0	1 (0.6)	1 (0.3)
Severe	0	0	0
Unknown	2	4	6
Missing	0	1	1
Prostate tenderness			
N	188	171	359
None	31 (16.5)	25 (14.6)	56 (15.6)
Mild	74 (39.4)	60 (35.1)	134 (37.3)
Moderate	61 (32.4)	70 (40.9)	131 (36.5)
Severe	22 (11.7)	16 (9.4)	38 (10.6)
Unknown	9	8	17
Missing	0	1	1
Perineal tenderness			
N	194	174	368
None	108 (55.7)	93 (53.4)	201 (54.6)
Mild	59 (30.4)	48 (27.6)	107 (29.1)
Moderate	20 (10.3)	29 (16.7)	49 (13.3)
Severe	7 (3.6)	4 (2.3)	11 (3.0)
Unknown	3	5	8
Missing	0	1	1

Adapted from Table 4 of CAPSS-101 Study Report

APPENDIX 4 CLINICAL SYMPTOMS AT ADMISSION

Clinical Symptoms at Admission of Intent-to Treat Population			
	Levofloxacin (197) N (%)	Ciprofloxacin (180) N (%)	Total (377) N (%)
Dysuria			
N	196	178	374
None	92 (46.9)	60 (33.7)	152 (40.6)
Mild	60 (30.6)	80 (44.9)	140 (37.4)
Moderate	34 (17.3)	30 (16.9)	64 (17.1)
Severe	10 (5.1)	8 (4.5)	18 (4.8)
Unknown	0	1	1
Missing	1	1	2
Frequency			
N	196	178	374
None	40 (20.4)	25 (14.0)	65 (17.4)
Mild	43 (21.9)	47 (26.4)	90 (24.1)
Moderate	78 (39.8)	82 (46.1)	160 (42.8)
Severe	35 (17.9)	24 (13.5)	59 (15.8)
Unknown	0	1	1
Missing	1	1	2
Urgency			
N	195	178	373
None	56 (28.7)	40 (22.5)	96 (25.7)
Mild	46 (23.6)	55 (30.9)	101 (27.1)
Moderate	66 (33.8)	62 (34.8)	128 (34.3)
Severe	27 (13.8)	21 (11.8)	48 (12.9)
Unknown	1	1	2
Missing	1	1	2
Hesitancy			
N	194	178	372
None	77 (39.7)	61 (34.3)	138 (37.1)
Mild	58 (29.9)	56 (31.5)	114 (30.6)
Moderate	48 (24.7)	46 (25.8)	94 (25.3)
Severe	11 (5.7)	15 (8.4)	26 (7.0)
Unknown	2	1	3
Missing	1	1	2
Low back pain			
N	195	177	372
None	81 (41.5)	62 (35.0)	143 (38.4)
Mild	46 (23.6)	47 (26.6)	93 (25.0)
Moderate	49 (25.1)	45 (25.4)	94 (25.3)
Severe	19 (9.7)	23 (13.0)	42 (11.3)
Unknown	1	2	3
Missing	1	1	2
Painful ejaculation			
N	185	169	354
None	101 (54.6)	99 (58.6)	200 (56.5)
Mild	42 (22.7)	30 (17.8)	72 (20.3)
Moderate	33 (17.8)	25 (14.8)	58 (16.4)
Severe	9 (4.9)	15 (8.9)	24 (6.8)
Unknown	10	10	20
Missing	2	1	3
Perineal discomfort			
N	196	178	374
None	75 (38.3)	69 (38.8)	144 (38.5)
Mild	51 (26.0)	56 (31.5)	107 (28.6)
Moderate	54 (27.6)	37 (20.8)	91 (24.3)
Severe	16 (8.2)	16 (9.0)	32 (8.6)
Unknown	0	1	1

Clinical Symptoms at Admission of Intent-to Treat Population			
	Levofloxacin (197) N (%)	Ciprofloxacin (180) N (%)	Total (377) N (%)
Missing	1	1	2
Decreased urinary stream			
N	196	178	374
None	79 (40.3)	56 (31.5)	135 (36.1)
Mild	47 (24.0)	66 (37.1)	113 (30.2)
Moderate	52 (26.5)	41 (23.0)	93 (24.9)
Severe	18 (9.2)	15 (8.4)	33 (8.8)
Unknown	0	1	1
Missing	1	1	2
Sense of incomplete voiding			
N	195	178	373
None	66 (33.8)	59 (33.1)	125 (33.5)
Mild	58 (29.7)	58 (32.6)	116 (31.1)
Moderate	47 (24.1)	43 (24.2)	90 (24.1)
Severe	24 (12.3)	18 (10.1)	42 (11.3)
Unknown	1	1	2
Missing	1	1	2
Fever			
N	193	179	372
None	174 (90.2)	165 (92.2)	339 (91.1)
Mild	14 (7.3)	9 (5.0)	23(6.2)
Moderate	5 (2.6)	4 (2.2)	9 (2.4)
Severe	0	1 (0.6)	1 (0.3)
Unknown	3	0	3
Missing	1	1	2
Chills			
N	194	179	373
None	183 (94.3)	163 (91.1)	346 (92.8)
Mild	9 (4.6)	10 (5.6)	19 (5.1)
Moderate	2 (1.0)	5 (2.8)	7 (1.9)
Severe	0	1 (0.6)	1 (0.3)
Unknown	2	0	2
Missing	1	1	2
Suprapubic discomfort			
N	195	178	373
None	94 (48.2)	92 (51.7)	186 (49.9)
Mild	60 (30.8)	49 (27.5)	109 (29.2)
Moderate	37 (19.0)	27 (15.2)	64 (17.2)
Severe	4 (2.1)	10 (5.6)	14 (3.8)
Unknown	1	1	2
Missing	1	1	2
Other			
N	36	36	64
Mild	22 (61.1)	22 (61.1)	31 (48.4)
Moderate	10 (27.8)	10 (27.8)	24 (37.5)
Severe	4 (11.1)	4 (11.1)	9 (14.1)

APPENDIX 5 TREATMENT-EMERGENT AEs RESULTING IN DISCONTINUATION OF THERAPY

Treatment-Emergent Adverse Events Resulting in Discontinuation of Therapy in Safety Evaluable Population

Treatment Patient No.	Age (yr)	Adverse Event (Verbatim) (Primary Term)	Severity	Study Day of Onset[a]	Relationship to Study Drug[b]	Duration of Therapy (Days)
Levofloxacin						
41903	66	Stomach Pain (Abdominal Pain)	Marked	3	Very Likely	6
		Restlessness (Agitation)	Moderate	3	Possible	
		Constipation (Constipation)	Marked	3	Very Likely	
46912	42	Rash all Over Body (Rash)	Moderate	2	Very Likely	8
46917	53	Bilateral Shoulder Soreness (Skeletal Pain)	Marked	2	Very Likely	7
51903	71	Hemorrhagic Brain Stem Infarct[c,d] (Haemorrhage Brain Stem)	Marked	25 (16 PT)	Not Related	9
60904	78	Malaise (Malaise)	Moderate	1	Possible	20
61901	52	Diarrhea (Diarrhoea)	Moderate	4	Very Likely	7
		Stomach Ache (Dyspepsia)	Marked	4	Very Likely	
		Vomiting (Vomiting)	Marked	7 (0 PT)	Very Likely	
87903	61	Abdominal Pain (Abdominal Pain)	Marked	5 (0 PT)	Very Likely	5
		Diarrhea (Diarrhoea)	Marked	5 (0 PT)	Very Likely	
87904	58	Hives (Urticaria)	Marked	1 (0 PT)	Very Likely	1
101913	61	Heartburn (Dyspepsia)	Moderate	18	Possible	19
106904	63	Stomach Pain (Abdominal Pain)	Mild	26 (1 PT)	Probable	25
109901	63	Headache (Headache)	Moderate	3 (0 PT)	Possible	3
		Nausea (Nausea)	Marked	3 (0 PT)	Possible	
Ciprofloxacin						
7940	70	Vomiting With Blood (Haematemesis)	Moderate	8	Possible	9
46916	63	Shortness Of Breath (Dyspnoea)	Marked	3	Possible	5
		Rash, Chest, Back, Face, Neck (Rash)	Marked	3	Very Likely	
46931	52	Joint Pain (Arthralgia)	Moderate	3	Probable	7

Treatment-Emergent Adverse Events Resulting in Discontinuation of Therapy in Safety Evaluable Population

Treatment Patient No.	Age (yr)	Adverse Event (Verbatim) (Primary Term)	Severity	Study Day of Onset[a]	Relationship to Study Drug[b]	Duration of Therapy (Days)
Ciprofloxacin (cont)						
48904	63	Fatigue (Fatigue)	Moderate	1 (0 PT)	Possible	1
		Fever (Fever)	Marked	2 (1 PT)	Possible	
		Headache (Headache)	Marked	1 (0 PT)	Possible	
		Body Aches (Malaise)	Marked	2 (1 PT)	Possible	
		Musculoskeletal Chest Pain (Myalgia)	Moderate	2 (1 PT)	Possible	
		Sleepiness (Somnolence)	Marked	1 (0 PT)	Possible	
49902	54	Hyperglycemia (Hyperglycaemia)	Mild	1	Possible	11
		Nausea (Nausea)	Mild	1	Possible	
60912	81	Dizziness (Dizziness)	Moderate	7	Possible	8
		Nausea (Nausea)	Moderate	7	Possible	
90901	62	(R) Shoulder Pain (Skeletal Pain)	Moderate	15 (0 PT)	Possible	15
94901	78	Abdominal Cramping (Abdominal Pain)	Moderate	2	Probable	3
		Constipation (Constipation)	Moderate	2	Probable	

[a] Relative to start of therapy.
[b] Based on investigator's assessment.
[c] Serious adverse event.
[d] Adverse event resulted in death.
NOTE: PT refers to the number of days since last day of active study drug administration (in Study Day of Onset column).

APPENDIX 6 SAFETY DEFINITIONS USED BY APPLICANT

Adverse events were defined as treatment-emergent signs and symptoms (events that were not present at admission, or events that represented an increase in severity or frequency of a sign or symptom already present at admission).

Drug related adverse events judged to have a probable or definite relationship to study drug.

Serious adverse events (prior to CAPSS-101) were defined as treatment-emergent adverse events that presented a significant threat to the well being of the subject. Serious adverse events included any event that was fatal, immediately life-threatening, permanently or significantly disabling, that required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment (greater than six months), required medical intervention to prevent permanent sequelae, or was a congenital anomaly, cancer, or an overdose.

Serious adverse event (CAPSS-101) was defined as any adverse event that was fatal, life-threatening (any adverse drug experience that placed the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred; i.e., it did not include a reaction that, had it occurred in a more severe form, might have caused death), required or prolonged inpatient hospitalization, resulted in a persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was deemed medically important (i.e., based on appropriate medical judgment, the event could jeopardize the subject and could require medical or surgical intervention to prevent one of the outcomes listed in this definition).

APPENDIX 7 MEAN VALUES AND MEAN CHANGES IN CLINICAL LABORATORY RESULTS

Mean Values and Mean Changes in Selected Clinical Laboratory Results Between Admission and Posttherapy in the Safety Evaluable Population

		Levofloxacin (N=197)				Ciprofloxacin (N=180)		
Laboratory Test	N	Admission Mean±SD	Posttherapy Mean±SD	Change Mean±SD	N	Admission Mean±SD	Posttherapy Mean±SD	Change Mean±SD
Hematology								
WBC (10^3/UL)	164	6.6±1.78	6.2±1.56	-0.3±1.55	142	7.4±11.89	7.3±12.52	-0.1±1.83
RBC (10^3/UL)	164	4.8±0.47	4.8±0.47	-0.0±0.21	142	4.8±0.41	4.8±0.41	0.0±0.21
HGB (g/dL)	164	14.7±1.12	14.6±1.14	-0.0±0.60	142	14.7±1.06	14.7±1.08	-0.0±0.62
HCT (%)	164	43.8±3.53	43.5±3.56	-0.3±2.23	142	44.0±3.15	43.9±3.22	-0.1±2.03
Platelet count (10^3/UL)	161	232.8±52.44	230.9±52.92	-1.9±26.03	136	234.9±56.00	234.9±54.24	-0.1±32.37
Lymphocytes (%)	164	30.1±8.43	31.8±8.58	1.7±7.40	142	31.7±10.04	32.2±8.92	0.5±7.75d
Monocytes (%)	164	6.7±2.74	6.8±2.15	0.2±2.58	142	6.8±2.43	7.0±2.28	0.2±2.50d
Eosinophils (%)	164	2.7±1.61	3.0±1.76	0.3±1.45	142	2.9±2.16	3.1±2.09	0.2±1.36d
Basophils (%)	164	0.4±0.24	0.4±0.22	-0.0±0.28	142	0.4±0.25	0.4±0.24	0.0±0.31d
Neutrophils (%)	164	60.2±9.46	58.0±9.34	-2.2±9.05	142	58.1±10.92	57.2±9.51	-1.0±9.91d
Blood Chemistry								
Sodium (mEq/L)	169	140.4±2.97	140.2±2.84	-0.2±3.26	150	140.1±2.75	140.3±2.71	0.2±3.23
Potassium (mEq/L)	169	4.5±0.43	4.4±0.38	-0.1±0.44	150	4.4±0.35	4.4±0.33	-0.0±0.34
Chloride (mEq/L)	169	102.8±2.87	102.9±2.73	0.0±2.99	150	102.5±2.86	102.7±2.83	0.2±3.15
Carbon dioxide (mEq/L)	169	24.1±2.45	23.9±2.43	-0.2±2.69	150	23.6±2.47	23.4±2.51	-0.3±2.81
Creatinine (mg/dL)	169	0.9±0.19	0.9±0.17	-0.0±0.13	150	0.9±0.19	0.9±0.18	-0.0±0.14
Blood urea nitrogen (mg/dL)	169	15.6±4.39	15.8±4.17	0.2±3.34	150	15.7±4.46	16.1±4.73	0.4±3.81
Uric acid (mg/dL)	169	6.1±1.36	6.1±1.46	0.1±0.89	150	5.9±1.38	6.0±1.50	0.1±0.77
Calcium (mg/dL)	169	9.4±0.49	9.4±0.47	-0.0±0.45	150	9.4±0.48	9.4±0.46	-0.0±0.45
Phosphorus ((mg/dL)	169	3.5±0.59	3.5±0.58	0.0±0.63	150	3.5±0.72	3.5±0.61	0.0±0.57
Total protein (g/dL)	169	7.3±0.48	7.2±0.50	-0.1±0.38	150	7.3±0.44	7.3±0.42	0.0±0.39
Albumin (g/dL)	169	4.2±0.26	4.1±0.25	-0.0±0.21	150	4.2±0.28	4.2±0.26	-0.0±0.21
Alkaline phosphatase (U/L)	169	75.8±22.52	74.4±20.75	-1.4±10.11	150	73.1±17.79	72.6±18.96	-0.6±8.48
Bilirubin, total (mg/dL)	169	0.5±0.24	0.5±0.22	0.0±0.17	150	0.5±0.33	0.5±0.36	0.0±0.19
AST (U/L)	169	24.1±12.51	25.7±34.68	1.5±35.76	150	21.9±7.68	22.4±6.60	0.5±7.81
LDH (U/L)	169	174.0±46.39	167.1±48.66	-6.9±41.71	150	168.2±42.12	165.5±31.26	-2.6±43.13
ALT (U/L)	169	29.3±29.39	25.8±15.12	-3.6±27.27	150	25.7±12.49	26.2±11.96	0.5±9.19
Glucose (mg/dL)	169	97.9±22.21	97.8±23.75	-0.1±26.45	150	99.0±25.96	102.3±27.32	3.3±22.94

Adapted from Table 38 of CAPSS-101 Study Report

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/s/

Maria Elena Ruiz
6/6/03 02:11:51 PM
MEDICAL OFFICER

Rigoberto Roca
6/10/03 12:35:56 PM
MEDICAL OFFICER

Renata Albrecht
6/11/03 12:04:10 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

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)*
The R.W. Johnson Pharmaceutical Research Institute
920 Route 202
P.O. Box 300
Raritan, NJ 08869-0602

4. SUBMISSION TYPE::
Prior Approval

5. SUPPLEMENT(S):

NUMBER(S):	DATE(S):
SE1-027	26-JUL-2002

6. NAME OF DRUG:
LEVAQUIN® Tablets

7. NONPROPRIETARY NAME:
levofloxacin tablets

8. SUPPLEMENT(S) PROVIDES FOR: The use of LEVAQUIN® Tablets in the treatment of chronic bacterial prostatitis utilizing a once daily 500-mg dose of levofloxacin.

9. AMENDMENTS/REPORTS:

10. PHARMACOLOGICAL CATEGORY:
Antibacterial

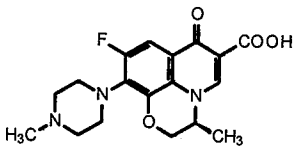
11. HOW DISPENSED:
[X] Rx [ ]OTC

12. RELATED IND/NDA/DMF(S):
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-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid



16. MEMORANDA:

EA consult to the Environmental Officer (N. Sager), 16-AUG-2002

17. COMMENTS: This supplemental NDA provides for the use of a 500-mg levofloxacin once daily 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 28-AUG-2002. The labeling submitted does not reflect the **recent agreement concerning changing the established name for the product supplied in pre-mix containers, namely "levofloxacin** in **5% dextrose".**

18. CONCLUSIONS AND RECOMMENDATIONS: The labeling should be updated to reflect the recent change in the established name for the pre-mix container. This 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
2/6/03 03:16:27 PM
CHEMIST

Norman Schmuff
2/9/03 10:10:29 AM
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) Tablets

NDA 20-634 / S-027
Treatment of chronic bacterial prostatitis

Food and Drug Administration
Center for Drug Evaluation and Research

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

Aug 28, 2002

Environmental Assessment Review #1, NDA 20-634 / S-027
Treatment of chronic bacterial prostatitis

LEVAQUIN® (levofloxacin) Tablets

SUMMARY

A FONSI is recommended

The environmental assessment (EA) dated July 10, 2002 supports the supplemental new drug application submitted by Johnson & Johnson Pharmaceutical R & D, LLC for Levaquin® (levofloxacin) Tablets. 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 and 4/17/2002. The most recent EA does not contain new or additional information beyond the new indication, chronic bacterial prostatitis. 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 and 7/16/02.

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 20634 / S-027

Treatment of chronic bacterial prostatitis

I. DATE: July 10, 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 (20-634/S-027) is requesting approval of levofloxacin for use in treatment of chronic bacterial prostatitis. 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 ——— kg. (Reference: Current EA dated July 10, 2002, page 155 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 and 4/17/02. 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 and 7/16/02.

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, March 31, 2000 and April 17, 2002.

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 60 ppb for the soil bacteria, *Bacillus subtilis*. The NOEC for daphnia magna was < 43 ppm. The NOEC for blue gill sunfish was 630 ppm

The EIC, namely 2.6 ppb, is 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 approval of the Rolling Supplement requesting approval for treatment of inhalation anthrax, post exposure, is pending.

Supplemental application (20-634/S-027) is requesting approval of levofloxacin for use in treatment of chronic bacterial prostatitis. 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: Confidential Appendix I in EA dated April 17, 2002 and July 10, 2002).

The EIC (aquatic) for levofloxacin based on NMT [redacted] er year remains unchanged [redacted] ıe FONSIs approved January 4, 2000, March 21, 2002 and July 16, 2002 were based on the exact same production estimate.)

New ecotoxicity data are not provided in an EA dated July 10, 2002.

The conclusion from the previous submissions that a FONSI is appropriate is still valid.

Review by: Florian Zielinski on Aug 28, 2002
Chemist, Center for Drug Evaluation and Research

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/s/

Florian Zielinski
8/30/02 09:22:36 AM
ENV ASSESSMENT

Nancy Sager
8/30/02 02:12:07 PM
ENV ASSESSMENT

Yuan-Yuan Chiu
9/16/02 09:40:21 AM
CHEMIST
Concurred

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

sNDA's: **20-634 (SE1-027) & 20-635 (SE1-026)**
Type of Submission: Supplemental Submissions
Review Number: 1
Date of Submission: 7/29/02
Information to Sponsor: Yes ( ) No (X)

Sponsor/Manufacturer:

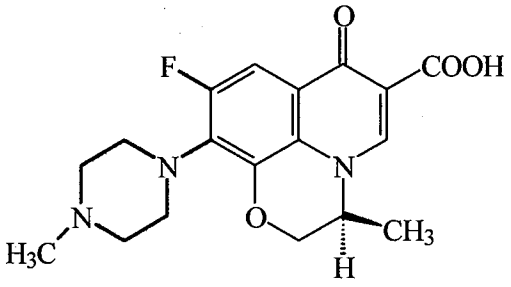
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Reviewer: Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer

Division; Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 3/6/03

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: Chronic Bacterial Prostatitis

Clinical Formualtion: Levaquin® Tablets (500mg); Levaquin® Injection (5 mg/ml and 25 mg/ml).

Route of Administration: Oral or Intravenous

Proposed Use: 500 mg levofloxacin daily for 28 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 pivotal Phase III clinical trials for chronic bacterial prostatitis at the dose level and duration sought in the proposed indication. 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:

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HFD-590/MO/S. Beidas
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HFD-590/Biopharm/P. Colangelo
HFD-590/Micro/P. Dionne
HFD-590/Chem/G. Holbert
HFD-590/Stat/K. Higgins

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/s/

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MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-634/SEI-027
20-635/SEI-026

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 26-JUL-02
CDER DATE: 29-JUL-02
REVIEW ASSIGN DATE: 31-JUL-02
REVIEW COMPLETE DATE: 25-SEP-02

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
Phone Number: (908) 704-4600

SUBMISSION REVIEWED: Supplemental Application for chronic bacterial prostatitis

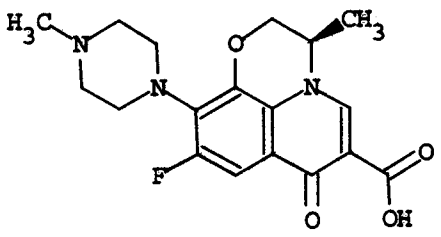
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Sinusitis, ABECB, CAP, Uncomplicated Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, Uncomplicated UTI, Complicated Skin and Skin Structure; Requesting chronic bacterial prostatitis

DOSAGE FORM: Levofloxacin tablets 250 mg, 500 mg and 750mg/tablet

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Tablets
NONPROPRIETARY/USAN: Levofloxacin tablets
CODE: RWJ-25213-097
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
STRUCTURAL FORMULA:



Molecular Formula: $C_{18}H_{20}FN_3O_4$
Molecular Weight: 361.38

SUPPORTING DOCUMENTS: **NDA 20-635—LEVAQUIN Injection.**

BACKGROUND:

The applicant has submitted a supplement to provide for use of levofloxacin in the treatment of chronic bacterial prostatitis utilizing a once daily 500 mg dose for 28 days. Study **CAPSS-101—A multicenter, double blind study to compare the safety and efficacy of** levofloxacin to that of ciprofloxacin in the treatment of chronic bacterial prostatitis has been presented. The proposed indication is further supported by a Phase I trial CAPSS-034 which evaluated the penetration of levofloxacin into the prostate of men undergoing transurethral prostaectomy.

Specific organisms for which coverage is requested are the gram-positive bacteria *Enterococcus faecalis, Staphylococcus epidermidis,* _____ and the gram-negative organism *Escherichia coli.*

CONCLUSIONS:

The supplemental application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The reviewing Medical Officer will need to decide whether enough evidence has been presented to grant an indication of chronic bacterial prostatitis and whether enough clinical evidence has been presented for each of the requested organisms. The required microbiology revisions are listed as recommendations at the end of this review on pages 31-37.

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EXECUTIVE SUMMARY

The applicant is requesting an indication of chronic bacterial prostatitis due to *Enterobacter faecalis. Escherichia coli, Staphylococcus epidermidis,*

Since *Enterococcus faecalis* and *Escherichia coli* are already in the clinical efficacy list (list #1) in the microbiology subsection of the label, the only changes needed are the addition of *Staphylococcus epidermidis,* his list. *In vitro* data have shown that methicillin-resistant strains of *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* have much higher levofloxacin MICs than do methicillin-susceptible strains of these species. The clinical trial included in this submission did not show efficacy against methicillin-resistant strains, therefore, these two species should be listed as methicillin-susceptible strains. *Streptococcus epidermidis* (methicillin-susceptible strains) and e will be deleted from the *in vitro* activity list since they will now be in the clinical efficacy list (list #1).

The Medical Officer will have to determine if enough evidence is presented to grant this indication and whether efficacy has been shown for each of the nine requested microorganisms.

PRECLINICAL EFFICACY *(IN VITRO)*

MECHANISM OF ACTION

No new information has been submitted.

IN VITRO ACTIVITY OF LEVOFLOXACIN AGAINST TARGET PATHOGENS

DATA FROM ORIGINAL NDA (EARLY 1990's)

The following data have been submitted to demonstrate that levofloxacin is active against organisms associated with chronic bacterial prostatitis. TABLE 1 summarizes data presented in the original NDA 20-634 for five of the six pathogens that the applicant is seeking. Levofloxacin MIC data was not present in the original NDA for This table compares the activity of levofloxacin with ciprofloxacin. NDA 20-634 was submitted in December 1995, therefore, data presented represents isolates collected and tested in the **early 1990's.**

TABLE 1 shows that in the early 1990's, the levofloxacin median MIC_{90} value for *Escherichia coli* was 0.10 µg/mL, which was below the 2 µg/mL breakpoint for susceptibility to levofloxacin. The ciprofloxacin median MIC_{90} for *E. coli* was 0.05 µg/mL, which was below the 1 µg/mL susceptible breakpoint for ciprofloxacin. For *Enterococcus faecalis, Streptococcus epidermidis,* and the levofloxacin median MIC_{90} values were 2, 1, and 2 µg/mL, respectively, which are equal to or less than the susceptible breakpoint of

2 µg/mL for levofloxacin. The ciprofloxacin median MIC_{90} values for *E. faecalis, S. epidermidis,* and *S. agalactiae* were all 2 µg/mL, which is the intermediate breakpoint for ciprofloxacin. Both levofloxacin and ciprofloxacin were less active against *Staphylococcus haemolyticus* with median MIC_{90} values of 16 and 32 µg/mL, respectively, which are above the resistant breakpoints of 8 µg/mL for levofloxacin and 4 µg/mL for ciprofloxacin.

TABLE 1
Antimicrobial Activity of Levofloxacin and Ciprofloxacin
(Data From Original NDA 20-634)

Organism	Quinolone	No of Isolates	MIC Range (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)
Escherichia coli	Levofloxacin	2510	≤0.006-32	0.03-1.56	0.10
	Ciprofloxacin	2480	≤0.004-32	0.015-0.78	0.05
Enterococcus faecalis	Levofloxacin	1220	0.25-128	1-25	2
	Ciprofloxacin	1189	0.25-128	1-25	2
Staphylococcus epidermidis	Levofloxacin	223	0.06-128	0.78-32	1
	Ciprofloxacin	223	≤0.03-32	0.78-8	2

DATA FROM LITERATURE SEARCH (1995-2002)

A literature search was conducted by the sponsor to identify publications from 1995-2002 reporting susceptibility data for levofloxacin when tested against any of the targeted organisms. TABLES 2-7 summarize the data available for each of the targeted species. In each of the tables below the weighted mean was determined by initially multiplying each trial mean by the number of isolates in the respective trial. The sum of these products was divided by the total number of isolates. The median MIC_{90}, however, is recognized as the standard by which antimicrobials are compared.

TABLE 2
Antimicrobial Activity of Levofloxacin Against
Escherichia coli (Literature Studies 1995-2002)

Investigator	Country	# Tested	Year Published	MIC_{50} (µg/mL)	MIC Range (µg/mL)	MIC_{90} (µg/mL)
Barry (1)	USA	30	1999	0.03	≤0.016->8.0	0.06
Blondeau (2)	Canada	37	2000	---	0.016-0.5	0.06
Child (3)	UK	49	1995	0.06	0.06-16	0.25
Cooper (4)	USA	2326	1996	---	≤0.5-8	≤0.5
Drago (5)	Italy	27	2001	0.016	0.004-2	0.06
Fung-Tomc (6)	USA	18	2000	0.03	0.016-0.06	0.06
Gilbert (7)	USA	20	2001	0.03	0.008-0.25	0.06
Hoban (10)	USA	356	2001	0.03	<0.03->4	0.5
Lopez (15)	Argentina	108	2001	0.03	≤0.004->32	16
Mascellino (16)	Italy	200	1998	0.06	≤0.015->32	8
Masuda (17)	Japan	42	1996	0.05	0.025-1.56	0.10
Matsuzaki (18)	Japan	50	1996	0.05	0.05-0.78	0.39
McCloskey (19)	USA	150	2000	0.03	≤0.016->16	0.06
Milatovic (20)	Netherlands	411	2000	0.03	≤0.008->16	8
Takahashi (24)	Japan	42	1997	0.05	0.025-1.56	0.10
Tanaka (25)	Japan	22	2002	0.015	≤0.004-2	0.5
Tsurumaki (26)	Japan	40	2000	0.025	0.012-25	0.39
Zhang (29)	China	100	1995	---	----	16
Total		**4028**	**Weighted Mean MIC_{90} = 2.39 µg/mL Median MIC_{90} = 0.39 µg/mL**			

The median MIC_{90} from 1995-2002 literature studies is 0.39 µg/mL. This has increased somewhat from the 0.10 µg/mL value reported in the original NDA. This value seems to have increased due to some foreign studies that have a higher MIC_{90} value than most United States studies. This may be due to the fact that isolates expressing extended spectrum β-lactamases (ESBLs) are usually resistant to most fluoroquinolones and these isolates are more often seen in foreign studies. Levofloxacin resistance in *Escherichia coli* appears to have only increased slightly since the original NDA submission.

TABLE 3
Antimicrobial Activity of Levofloxacin Against
Enterococcus faecalis (Literature Studies 1995-2002)

Investigator	Country	# Tested	Year Published	MIC_{50} (µg/mL)	MIC Range (µg/mL)	MIC_{90} (µg/mL)
Barry (1)	USA	30	1999	1	0.25->8.0	>8
Blondeau (2)	Canada	11	2000	---	1-≥16	8
Child (3)	UK	15	1995	1	0.5-2	2
Cooper (4)	USA	1005	1996	1	0.5->16	>16
Drago (5)	Italy	26	2001	1	1-≥8	≥8
Fung-Tomc (6)	USA	18	2000	1	1-32	2
Hoban (10)	USA	131	2001	1	0.12->16	>16
HoogKamp (11)	Netherlands	25	2000	1	0.5-≥32	≥32
Lopez (15)	Argentina	98	2001	1	0.125->32	>32
Masuda (17)	Japan	30	1996	0.78	0.39-3.13	1.56
Matsuzaki (18)	Japan	25	1996	0.78	0.78-25	25
McCloskey (19)	USA	81	2000	1	0.5->16	>16
Milatovic (20)	Netherlands	230	2000	1	0.25->16	16
Montanari (21)	Italy	19	1999	1	0.5-32	16
Okamoto (22)	Japan	9	2000	1	---	64
Takahashi (24)	Japan	30	1997	0.78	0.39-3.13	1.56
Tanaka (25)	Japan	25	2002	1	0.5-64	32
Tsurumaki (26)	Japan	75	2000	3.13	0.78->100	50
Total		**1883**	**Weighted Mean MIC_{90} = 17.97 µg/mL Median MIC_{90} = 16 µg/mL**			

The median MIC_{90} from 1995-2002 literature studies is 16 µg/mL. This has increased from the 2 µg/mL value reported in the original NDA. Many strains have become resistant to **levofloxacin since the early 1990's when the drug was first approved. Most of the MIC_{50}** values are still in the susceptible range, therefore, most strains are still susceptible to levofloxacin.

TABLE 4
Antimicrobial Activity of Levofloxacin Against
Staphylococcus epidermidis (Literature Studies 1995-2002)

Investigator	Country	# Tested	Year Published	MIC_{50} (µg/mL)	MIC Range (µg/mL)	MIC_{90} (µg/mL)
Barry (1)	USA	25	1999	0.25	0.06-0.5	0.25
Cooper (4)	USA	533	1996	2	0.5-16	16
Drago (5)	Italy	20	2001	0.125	0.125-≥8	≥8
Fung-Tomc (6)	USA	10 MS	2000	0.25	0.12-0.25	0.25
		17 MR		0.25	0.12-8	8
Goldstein (8)	USA	10	1998	0.125	0.125-0.25	0.125
Goldstein (9)	USA	11	2001	0.25	0.125-0.25	0.25
Hoban (10)	USA	119	2001	2	0.03->4	16
HoogKamp (11)	Netherlands	33 QS	2000	0.12	0.12-1	0.25
		10 QR		8	0.5-≥32	≥32
Mascellino (16)	Italy	200	1998	0.5	0.03->32	8
Masuda (17)	Japan	30	1996	3.13	0.10->100	100
Matsuzaki (18)	Japan	25	1996	0.39	0.20->100	6.25
McCloskey (19)	USA	70	2000	4	0.12-32	16
Milatovic (20)	Netherlands	214 MS	2000	0.12	0.12-16	4
		436 MR		4	0.03->16	>16
Takahashi (24)	Japan	30	1997	3.13	0.10->100	100
Yamakawa (28)	Japan	27	2002	0.20	0.10-0.39	0.20
		26 MR		3.13	3.13-25	25
Total (MR, QR not included)		**1357**	**Weighted Mean MIC_{90} = 15.0 µg/mL Median MIC_{90} = 6.25 µg/mL**			

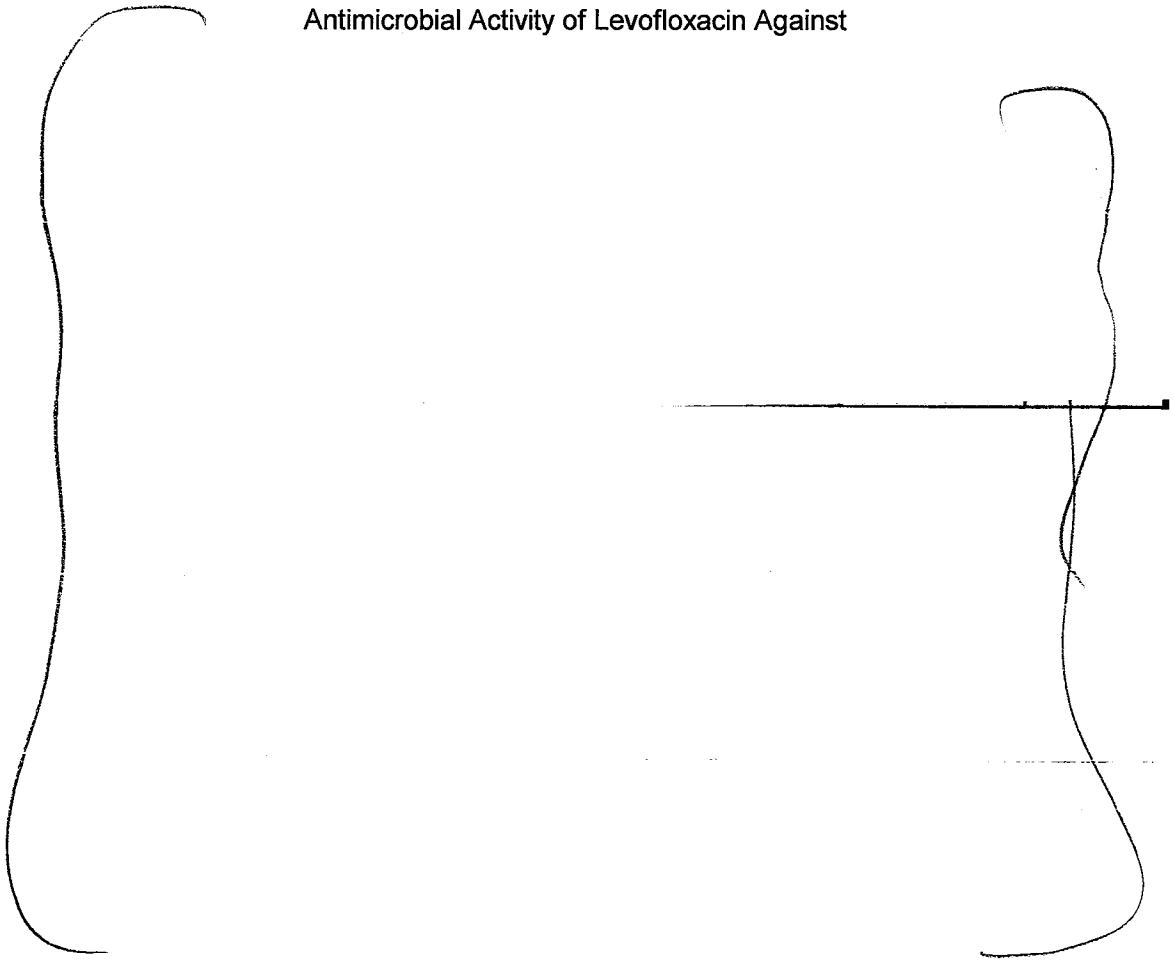
MS = methicillin-susceptible; MR = methicillin-resistant
QS = quinolone-susceptible; QR = quinolone-resistant

The median MIC_{90} from 1995-2002 literature studies is 6.25 µg/mL. This has increased from the 1.0 µg/mL value reported in the original NDA. In most studies the methicillin-resistant strains were not separated from the methicillin-susceptible strains. Most of these methicillin-resistant strains are also quinolone-resistant and have a much higher MIC **than the susceptible strains. In the early 1990's there were not as many of these** methicillin/quinolone resistant strains as there are now. In the few studies where the **methicillin-susceptible and –resistant strains were separated it can be seen that the** methicillin-susceptible strains usually had a MIC_{90} value of 0.25 µg/mL. This species should **be separated into methicillin-susceptible and –resistant strains and only methicillin-susceptible** strains should be listed as susceptible to levofloxacin.

TABLE 5
Antimicrobial Activity of Levofloxacin Against

TABLE 6
Antimicrobial Activity of Levofloxacin Against

TABLE 7
Antimicrobial Activity of Levofloxacin Against



DATA FROM CLINICAL STUDIES

This supplement has one new study CAPSS-101. This randomized, active controlled, double-blind Phase III trial was designed to evaluate the safety and efficacy of levofloxacin 500 mg administered orally once daily for 28 days in the treatment of chronic bacterial prostatitis. In the study, levofloxacin was compared with ciprofloxacin 500 mg administered orally twice a day for 28 days. The MIC susceptibility data was determined by broth microdilution assays for the six pathogens. The MIC range for testing levofloxacin was ≤1 to ≥8 µg/mL, and the MIC range for testing ciprofloxacin was ≤0.5 to ≥4 µg/mL. TABLE 8 presents these data.

TABLE 8
Antimicrobial Activity of Levofloxacin and Comparators Against
Clinical Isolates from Study CAPSS-101

Organism	Quinolone	No of Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Escherichia coli	Levofloxacin	30	≤1-≥8	≤1	≤1
	Ciprofloxacin	30	≤0.5-≥4	≤0.5	1
Enterococcus faecalis	Levofloxacin	117	≤1-≥8	≤1	≤1
	Ciprofloxacin	117	≤0.5-≥4	≤0.5	1
Staphylococcus epidermidis	Levofloxacin	66	≤1-≥8	≤1	≥8
	Ciprofloxacin	66	≤0.5-≥4	≤0.5	≥4

The levofloxacin MIC_{90} values in TABLE 8 demonstrate susceptibility below the susceptible breakpoint of 2 µg/mL for *E. coli, E. faecalis*. MIC_{90} values for the *Staphylococcus* species are above the susceptible breakpoint. The MIC_{50} values for the *Staphylococcus* species are, however below the susceptible breakpoint for levofloxacin. The majority of *Staphylococcus epidermidis* and *us* isolates were, therefore, susceptible to levofloxacin.

PHARMACOKINETICS/BIOAVAILABILITY

The information in this section is taken from the studies submitted by the applicant and has not been reviewed by a FDA Biopharmaceutical Reviewer, as of the date of this review.

Study CAPSS-034 was performed to determine the extent of penetration of levofloxacin into the site of prostate infection. The objectives of the study were to determine the concentration of levofloxacin in prostatic tissue, plasma, and cerebrospinal fluid (CSF) following three 500-mg daily doses, two oral and one parenteral, and to further support the safety profile of the drug.

This was a noncomparative, open-label, randomized Phase I study conducted in the United States. Approximately 24 men who were scheduled to undergo elective transurethral prostectomy under spinal anesthesia were enrolled. A spinal fluid sample was drawn at the time of the spinal tap before anesthesia was administered. A prostatic tissue sample was obtained at the time of surgery. The prostatic tissue samples were collected at four specific times (0-0.5, 3.75-4.25, 7.5-8.5, or 24 hours) after the end of the intravenous infusion of the last dose of levofloxacin. Blood samples were collected immediately before infusion of levofloxacin on Day 3, immediately after infusion, and at 1.5, 2.0, 3.75, 5.0, and 6.0 hours following infusion. Blood samples were also collected at the time of CSF collection and prostate tissue collection.

Twenty-two subjects completed the study. Prostate levofloxacin concentration was measured but not included for one subject (subject requested not to be used). Another subject was not included because prostate levofloxacin concentration was quite low as was a simultaneous plasma concentration. A regularly scheduled plasma sample taken 42 minutes later revealed a plasma levofloxacin concentration over sevenfold higher than the previous plasma sample level. The prostate/plasma penetration ratio calculated from mean pharmacokinetic parameters was 2.96 in this study. This indicates that levofloxacin penetrates into prostate tissue at levels that are higher on average than those in serum.

RESULTS FROM CLINICAL TRIALS

STUDY CAPSS-101

Study CAPSS-101 evaluates the efficacy of levofloxacin 500 mg orally given once daily for the treatment of chronic bacterial prostatitis. This was a multicenter, randomized, double-blind, active-controlled clinical study conducted in the United States. Subjects were assigned to one of two treatment groups (levofloxacin or ciprofloxacin) in a 1:1 ratio according to a computer-generated randomization schedule and according to whether the subject enrolled in the study based on white blood cell (WBC) count in the voided bladder 3 (VB_3) specimen or microbiological culture results from the expressed prostatic fluid (EPS) or VB_3 specimens. The primary objective of this study was to evaluate the safety and efficacy of levofloxacin 500 mg orally given once daily compared to ciprofloxacin 500 mg orally given twice a day for four-weeks in the treatment of chronic bacterial prostatitis.

To be admitted into the study subjects had to meet the following criteria:

- Males 18 years of age or older;
- Clinical diagnosis of chronic prostatitis determined by the following three criteria:
  - Clinical signs and symptoms of prostatitis; and
  - History of chronic prostatitis defined as one previous clinical diagnosis of prostatitis for a symptomatic episode that lasted at least four weeks or two or more episodes of any duration during the previous year; and
  - Laboratory evidence of prostatitis base on one of the following definitions:
    - VB_3 specimen containing ≥ 10 times the WBC count of VB_2;
    - VB_3 or EPS specimen containing $\geq 10^2$ colony-forming units (CFUs) of a single bacterial strain if the VB_2 specimen was sterile;
    - VB_3 or EPS specimen containing ≥ 10 times the bacterial count (CFUs) of VB_2;
    - VB_3 or EPS specimen containing $\geq 10^2$ bacterial count (CFUs) of a bacterial strain that was different from any present in VB_2 and was recognized as a uropathogen.

The primary efficacy endpoint was microbiological response of each subject's infection at the posttherapy (test-of-cure) visit based on microbiologically evaluable subjects. Secondary efficacy variables included the posttherapy microbiologic response by pathogen identified at admission, the one-month poststudy assessment of microbiologic relapse by subjects infections, the one-month poststudy assessment of microbiologic relapse by pathogen identified at admission, clinical cure posttherapy, and clinical success posttherapy.

Three hundred eighty-three subjects (383) were enrolled in the study and assigned to receive levofloxacin (199 subjects) or ciprofloxacin (184 subjects). Six subjects (two on levofloxacin and four on ciprofloxacin) did not receive drugs. There were, therefore, 197 subjects in the levofloxacin group and 180 subjects in the ciprofloxacin group in the intent-to-treat (ITT) population. Of the 197 subjects in the levofloxacin treatment group, 172 (87.3%) completed therapy and 25 (12.7%) discontinued therapy prematurely. Of the 180 subjects in the ciprofloxacin treatment group, 153 (85.0%) completed therapy and 27 (15.0%) discontinued therapy prematurely. Of those randomized and treated, 170 subjects in the levofloxacin group and 151 in the ciprofloxacin group had an admission pathogen and were, therefore, included in the modified ITT population. One hundred thirty-six (136) levofloxacin treated subjects and 125 ciprofloxacin treated subjects were evaluable for microbiological efficacy. In the levofloxacin treatment group, 134 subjects were eligible for the one-month poststudy evaluation (i.e. clinically cured or improved at the posttherapy visit), and 118 subjects completed the one-month poststudy evaluation. In the ciprofloxacin treatment group, 125 subjects were eligible for the one-month poststudy evaluation, and 107 completed the one-month poststudy evaluation. TABLE 9 gives a summary of the reasons for microbiological nonevaluablility.

TABLE 9
Summary of Primary Reason for Microbiological Nonevaluablility
(Intent-to-Treat Population—Study CAPSS 101)

Reason	Levofloxacin (N =197) n	(%)	Ciprofloxacin (N = 180) n	(%)
Microbiologic subjects				
Total # of microbiologic subjects (modified ITT)	170		151	
Microbiologically evaluable population	136	(80.0)	125	(82.8)
Excluded from microbiologically evaluable population	34	(20.0)	26	(17.2)
Insufficient course of therapy	13	(7.6)	7	(4.6)
Course of therapy too long	3	(1.8)	5	(3.3)
Effective concomitant therapy	0	(0.0)	0	(0.0)
Lost to follow-up	2	(1.2)	2	(1.3)
Admission culture not with 5 days pretherapy	5	(2.9)	2	(1.3)
No posttherapy culture between Days 5-18	10	(5.9)	10	(6.6)
Other protocol violation	1	(0.6)	0	(0.0)

TABLE 10 presents a summary of the *in vitro* susceptibility of pathogens isolated at admission from microbiologically evaluable subjects in each treatment group. A total of 406 pathogens were isolated; 213 were isolated from 136 subjects in the levofloxacin treatment group and 193 from 125 subjects in the ciprofloxacin treatment group. Three hundred ninety-seven pathogens (levofloxacin 209; ciprofloxacin 188) were tested for susceptibility to study drugs.

TABLE 10
In vitro Susceptibility of Pathogens Isolated at Admission
Microbiologically Evaluable Population
(Study CAPSS-101)

Susceptibility of Pathogen	No. (%) of Pathogens	
	Levofloxacin	Ciprofloxacin
Susceptible	192 (91.9)	160 (85.1)
Intermediate	9 (4.3)	5 (2.7)
Resistant	8 (3.8)	23 (12.2)
Unknown	4	5
Total No. Pathogens	213	193

The cross-susceptibilities of admission pathogens to the two study drugs in microbiologically evaluable subjects are presented in TABLE 11. Of the 406 pathogens isolated, 353/358 (98.6%) pathogens that were sensitive to levofloxacin were sensitive or intermediate to ciprofloxacin, and 5/358 (1.4%) were resistant to ciprofloxacin. Similarly, 342/345 (99.1%) pathogens that were sensitive to ciprofloxacin were sensitive or of intermediate sensitivity to levofloxacin and 3/345 (0.9%) were resistant to levofloxacin.

TABLE 11
Cross-Susceptibility of Pathogens Isolated at Admission
Microbiologically Evaluable Population
(Study CAPSS-101)

		CIPROFLOXACIN			
	S	I	R	U	TOTAL
LEVOFLOXACIN S	341	12	5	0	358
LEVOFLOXACIN I	1	1	13	0	15
LEVOFLOXACIN R	3	0	21	0	24
LEVOFLOXACIN U	0	0	0	9	9
LEVOFLOXACIN TOTAL	345	13	39	9	406

TABLE 12 presents the posttherapy (5-18 days after therapy) microbiological **eradication rates by subject's infection (all the subject's pathogens isolated at admission) for** each treatment group for microbiologically evaluable subjects. TABLE 13 presents the same data for the modified intent-to-treat (mITT) population.

TABLE 12
Posttherapy Microbiological Rates by Subjects' Infection
Subjects Evaluable for Microbiological Efficacy

Levofloxacin No. (%)			Ciprofloxacin No. (%)		
No.	Eradicated	Persisted	No.	Eradicated	Persisted
136	102 (75.0)	34 (25.0)	125	96 (76.8)	29 (23.2)

TABLE 13
Posttherapy Microbiological Rates by Subjects' Infection
Modified Intent-to-Treat Population

Levofloxacin No. (%)				Ciprofloxacin No. (%)			
No.	Eradicated	Persisted	Unknown	No.	Eradicated	Persisted	Unknown
170	119 (70.0)	37 (21.8)	14 (8.2)	151	109 (72.2)	31 (20.5)	11 (7.3)

Microbiological eradication rates at posttherapy visit for microbiologically evaluable subjects by pathogen are presented in TABLE 14. Data are presented for pathogens that were isolated 10 or more times in either treatment group. The overall microbiological eradication rate by pathogen was 80.8% (172/213) in the levofloxacin treatment group and 82.9% (160/193) in the ciprofloxacin treatment group. Microbiological eradication rates for frequently isolated pathogens ranged from 72.2% to 93.3% in levofloxacin-treated subjects and from 75.0% to 100.0% in ciprofloxacin-treated subjects.

In the levofloxacin treatment group, 25 pathogens were demonstrated to persist and two pathogens persisted with acquisition of resistance to levofloxacin. The resistant organisms were [redacted] MIC ≥8 µg/mL) and coagulase-negative staphylococci (MIC ≥8 µg/mL). In the ciprofloxacin treatment group, 15 pathogens persisted and four pathogens persisted with acquisition of resistance to ciprofloxacin. The resistant organisms were [redacted] three isolates all with a MIC ≥4 µg/mL) and *Staphylococcus epidermidis* (one isolated with a MIC ≥4 µg/mL).

TABLE 15 shows the microbiological eradication rates at posttherapy for the modified intent-to-treat population (mITT). Data are presented for pathogens that were isolated 10 or more times in either treatment group. The overall microbiological eradication rate by pathogen was 75.7% (199/263) in the levofloxacin treatment group and 78.8% (186/236) in the ciprofloxacin treatment group. Microbiological eradication rates for frequently isolated pathogens ranged from 66.7% to 90.9% in levofloxacin-treated subjects and from 70.4% to 100.0% in ciprofloxacin-treated subjects. The only organisms that persisted with acquisition of resistance were the ones seen in the microbiologically evaluable population.

TABLE 14
Microbiological Response Rates by Pathogen for Frequently Isolated Pathogens
Microbiologically Evaluable Population
(Study CAPSS-101)

	Levofloxacin (N = 136) No. (%)				Ciprofloxacin (N =125) No. (%)			
Admission Pathogen	No.	Eradicated	Persisted	Unknown	No.	Eradicated	Persisted	Unknown
Escherichia coli	15	14 (93.3)	1 (6.7)	0 (0.0)	11	9 (81.8)	2 (18.2)	0 (0.0)
Staphylococcus epidermidis	24	20 (83.3)	4 (16.7)	0 (0.0)	29	26 (89.7)	3 (10.3)	0 (0.0)
Enterococcus faecalis	54	39 (72.2)	15 (27.8)	0 (0.0)	45	34 (75.6)	11 (24.4)	0 (0.0)
Total pathogens	213	172 (80.8)	41 (19.2)	0 (0.0)	193	160 (82.9)	33 (17.1)	0 (0.0)

Results are shown for specific pathogens only if isolated 10 or more times in either treatment group
Total pathogens includes are all isolated pathogens even if not isolated 10 or more times

TABLE 15
Microbiological Response Rates by Pathogen for Frequently Isolated Pathogens
Modified Intent-to-Treat Population (mITT)
(Study CAPSS-101)

	Levofloxacin (N = 170) No. (%)				Ciprofloxacin (N =151) No. (%)			
Admission Pathogen	No.	Eradicated	Persisted	Unknown	No.	Eradicated	Persisted	Unknown
Escherichia coli	18	16 (88.9)	1 (5.6)	1 (5.6)	12	9 (75.0)	2 (16.7)	1 (8.3)
Staphylococcus epidermidis	31	23 (74.2)	4 (12.9)	4 (12.9)	37	30 (81.1)	3 (8.1)	4 (10.8)
Enterococcus faecalis	54	44 (81.5)	7 (13.0)	3 (5.6)	54	38 (70.4)	13 (24.0)	3 (5.6)
Total pathogens	263	199 (75.7)	44 (16.7)	20 (7.6)	236	186 (78.8)	35 (14.8)	15 (6.4)

Results are shown for specific pathogens only if isolated 10 or more times in either treatment group
Total pathogens includes are all isolated pathogens even if not isolated 10 or more times

Poststudy (24 to 45 days after the last dose of drug) microbiological rates by **subject's infections for the microbiologically evaluable population are presented in** TABLE 16. These rates were determined for subjects who had a posttherapy response of cured or improved and who came in for a poststudy visit.

Among 102 subjects treated with levofloxacin, 61.8% (63/102) had a response of long-term eradication (includes presumed eradication) and 15.7% (16/102) had a response of persisted (includes presumed persisted); 12 of these 16 subjects (75%) were considered clinical cures. Fifteen (14.7%) of the 102 subjects had a response of relapse. Eight (7.8%) of the 102 subjects had an unknown response. Among 91 subjects treated with ciprofloxacin, 74.7% (68/91) had a response of long-term eradication (includes presumed eradication) and 7.7% (7/91) had a response of persisted (includes presumed persisted); five of these 7 subjects (71.4%) were considered clinical cures. Nine (9.9%) of the 91 subjects had a response of relapse. Seven (7.7%) of the 91 subjects had an unknown response.

TABLE 16
Poststudy Microbiological Response Rates by Subject's Infection
Microbiologically Evaluable Population

Levofloxacin (N=102) No. (%)				Ciprofloxacin (N=91) No. (%)			
Eradicated	Persisted	Relapse	Unknown	Eradicated	Persisted	Relapse	Unknown
63 (61.8)	16 (15.7)	15 (14.7)	8 (7.8)	68 (74.7)	7 (7.7)	9 (9.9)	7 (7.7)

Poststudy microbiological rates by subject's infection for the mITT population are presented in TABLE 17.

TABLE 17
Poststudy Microbiological Response Rates by Subject's Infection
Modified Intent-to-Treat Population (mITT)

Levofloxacin (N=119) No. (%)				Ciprofloxacin (N=107) No. (%)			
Eradicated	Persisted	Relapse	Unknown	Eradicated	Persisted	Relapse	Unknown
72 (60.5)	17 (14.3)	17 (14.3)	13 (10.9)	78 (72.9)	7 (6.5)	11 (10.3)	11 (10.3)

Poststudy microbiological response rates by pathogen for frequently isolated pathogens in microbiologically evaluable subjects are presented in TABLE 18. With levofloxacin treatment, the most prevalent pathogen, *Enterococcus faecalis,* persisted in 22.0% (9/41) of cases and relapsed in 9.8% (4/41) of cases. Other prevalent pathogens were *Staphylococcus epidermidis,*

and *Escherichia coli. Staphylococcus epidermidis* persisted in 6.3% (1/16) cases and relapsed in 12.5% (2/16) cases rsisted in 13.3% (2/15) cases and relapsed in 6.7% (1/15) cases sisted in 26.7% (4/15) cases and relapsed in 13.3% (2/15) cases. *E. coli* relapsed in 28.6% (4/14) cases; there were no cases of persistence.

With ciprofloxacin treatment, *E. faecalis* persisted in 3.1% (1/32) cases and relapsed in 6.3% (2/32) cases. *S. epidermidis* persisted in 8.0% (2/25) cases and relapsed in 12.0% (3/25) cases. [illegible]ersisted in 16.7% (2/12) cases; there were no cases of relapse. *S. agalactiae* persisted in 13.3% (2/15) cases and relapsed in 20.0% (3/15) cases. There were no cases of persistence or relapse with *E. coli*.

TABLE 18
Microbiological Response Rates by Pathogen Poststudy for Frequently Isolated Pathogens—Microbiologically Evaluable Population

		Eradicated		Persisted		Relapse		Unknown	
Admission Pathogen	No.	n	(%)	n	(%)	n	(%)	n	(%)
Levofloxacin (N=102)									
Escherichia coli	14	9	(64.3)	0	(0.0)	4	(28.6)	1	(7.1)
Staphylococcus epidermidis	16	11	(68.8)	1	(6.3)	2	(12.5)	2	(12.5)
Enterococcus faecalis	41	24	(58.5)	9	(22.0)	4	(9.8)	4	(9.8)
Ciprofloxacin (N=91)									
Escherichia coli	7	6	(85.7)	0	(0.0)	0	(0.0)	1	(14.3)
Staphylococcus epidermidis	25	19	(76.0)	2	(8.0)	3	(12.0)	1	(4.0)
Enterococcus faecalis	32	25	(78.1)	1	(3.1)	2	(6.3)	4	(12.5)

Results are shown for specific pathogens only if isolated 10 or more times in either treatment group

Poststudy microbiological response rates by pathogen for frequently isolated pathogens in the modified intent-to-treat population are presented in TABLE 19. With levofloxacin treatment, the most prevalent pathogen, *Enterococcus faecalis,* persisted in 21.3% (10/47) of cases and relapsed in 10.6% (5/47) of cases. Other prevalent pathogens were *Staphylococcus epidermidis,* and *Escherichia coli*. *Staphylococcus epidermidis* persisted in 5.3% (1/19) cases and relapsed in 10.5% (2/19) cases [illegible]ersisted in 12.5% (2/16) cases and relapsed in 6.3% (1/16) cases. [illegible]ersisted in 25.0% (4/16) cases and relapsed in 18.8% (3/16) cases. *E. coli* relapsed in 26.7% (4/15) cases; there were no cases of persistence.

With ciprofloxacin treatment, *E. faecalis* persisted in 2.6% (1/39) cases and relapsed in 7.7% (3/39) cases. *S. epidermidis* persisted in 6.5% (2/31) cases and relapsed in 16.1% (5/31) cases. [illegible]ersisted in 12.5% (2/16) cases; there were no cases of relapse. [illegible]sisted in 11.8% (2/17) cases and relapsed in 17.6% (3/17) cases. *E. coli* relapsed in 12.5% (1/8) cases; there were no cases of persistence.

TABLE 19
Microbiological Response Rates by Pathogen Poststudy for Frequently **Isolated Pathogens—Modified Intent-to-Treat Population (mITT)**

		Eradicated		Persisted		Relapse		Unknown	
Admission Pathogen	No.	n	(%)	n	(%)	n	(%)	n	(%)
Levofloxacin (N=119)									
Escherichia coli	15	10	(66.7)	0	(0.0)	4	(26.7)	1	(6.7)
Staphylococcus epidermidis	19	14	(73.7)	1	(5.3)	2	(10.5)	2	(10.5)
Enterococcus faecalis	47	26	(55.3)	10	(21.3)	5	(10.6)	6	(12.8)
Ciprofloxacin (N=107)									
Escherichia coli	8	6	(75.0)	0	(0.0)	1	(12.5)	1	(12.5)
Staphylococcus epidermidis	31	23	(74.2)	2	(6.5)	5	(16.1)	1	(3.2)
Enterococcus faecalis	39	29	(74.4)	1	(2.6)	3	(7.7)	6	(15.4)

Results are shown for specific pathogens only if isolated 10 or more times in either treatment group

TABLE 20 lists the subjects (17 levofloxacin-treated and 11 ciprofloxacin treated) with a response of microbiological relapse at the poststudy visit for all subjects with an admission pathogen (modified ITT population). The pathogens isolated, type of specimen, microbiological response poststudy, and admission susceptibility are provided. For mITT subjects with microbiological relapse in the levofloxacin treatment group, all admission pathogens with the exception of one, were susceptible with an MIC of ≤1 µg/mL. One subject (62928) had a resistant *E. coli* (MIC ≥8 µg/mL) at admission that was eradicated poststudy. For mITT subjects with microbiological relapse in the ciprofloxacin treatment group, most admission pathogens were susceptible (MICs ≤0.5 to 1 µg/mL). The admission pathogens (*Staphylococcus* and *Streptococcus* unspeciated) for one subject (29902) were of unknown susceptibility. One admission pathogen [redacted] for subject 7914 was resistant (MIC 4.0 µg/mL) and one admission pathogen [redacted] for subject 51990 was of intermediate susceptibility.

TABLE 20
Subjects with a Microbiological Relapse at Poststudy
Modified Intent-to-Treat Population

Treatment Subject	Population	Admission Pathogen	Micro Response Poststudy	Type of Specimen	Admission Susceptibility	Admission MIC (µg/mL)	Admission Disk (mm)
Levofloxacin							
1902	MBE	*Escherichia coli*	Pr. Rlps	VB_3	Susceptible	≤1	
7902	MBE	*Escherichia coli*	Pr. Rlps	EPS	Susceptible	≤1	
		Enterococcus faecalis	Pr. Rlps	EPS	Susceptible	≤1	
7923	MBE	*Citrobacter diversus*	Pr. Rlps	EPS	Susceptible	≤1	
		Enterococcus faecalis	Pr. Rlps	EPS	Susceptible	≤1	
13903	MBE	*S. epidermidis*	Pr. Rlps	EPS	Susceptible	≤1	
		S. hominis	Pr. Rlps	EPS	Susceptible	≤1	
17916	MBE	*S. haemolyticus*	Pr. Rlps	EPS	Susceptible	≤1	
29907	MBE	*Enterococcus faecalis*	Relapse	EPS	Susceptible		18
32901	mITT	*S. agalactiae*	Relapse	EPS	Susceptible		18
46905	MBE	*Escherichia coli*	Pr. Rlps	EPS	Susceptible	≤1	
46926	MBE	*Escherichia coli*	Pr. Rlps	EPS	Susceptible	≤1	
		S. agalactiae	Pr. Rlps	VB_3	Susceptible	≤1	
		S. mitis	Pr. Rlps	VB_3	Susceptible	0.5	
48902	MBE	Staph coag-neg	Pr. Rlps	VB_3	Susceptible	≤1	
		Streptococcus bovis	Pr. Rlps	VB_3	Susceptible		21
51907	MBE	*A. calcoaceticus*	Pr. Rlps	VB_3	Susceptible	≤1	
62922	MBE	*Enterococcus faecalis*	Pr. Rlps	EPS	Susceptible	≤1	
62928	mITT	*Escherichia coli*	Eradicated	EPS	Resistant	≥8	
		Enterococcus faecalis	Relapse	EPS	Susceptible	≤1	
70903	MBE	*S. agalactiae*	Pr. Rlps	EPS	Susceptible	≤1	
90903	MBE	*S. agalactiae*	Eradicated	VB_3	Susceptible	≤1	
		Enterococcus faecalis	Relapse	EPS	Susceptible	≤1	
94907	MBE	*S. agalactiae*	Relapse	VB_3	Susceptible	≤1	
108901	MBE	*S. epidermidis*	Relapse	VB_3	Susceptible	≤1	
		Enterococcus faecalis	Eradicated	EPS	Susceptible	≤1	

MBE = Microbiologically Evaluable; mITT = Modified Intent-to-Treat
Pr. Rlps = presumed relapse
EPS = Expressed prostatic secretions
VB_3 = Voided bladder 3-first 5-10 mL of urine stream immediately after prostatic massage

TABLE 20 (Continued)
Subjects with a Microbiological Relapse at Poststudy
Modified Intent-to-Treat Population

Treatment Subject	Population	Admission Pathogen	Micro Response Poststudy	Type of Specimen	Admission Susceptibility	Admission MIC (µg/mL)	Admission Disk (mm)
Ciprofloxacin							
7914	MBE	*S. maltophilia*	Pr. Rlps	EPS	Resistant	4.0	
		S. agalactiae	Pr. Rlps	EPS	Susceptible	0.38	
		S. acidominimus	Pr. Rlps	VB_3	Susceptible	0.064	
		S. uberis	Pr. Rlps	EPS	Susceptible	0.75	
19906	MBE	*S. equinus*	Pr. Rlps	EPS	Susceptible	0.75	
28903	MBE	Staph coag-neg	Pr. Rlps	EPS	Susceptible	≤0.5	
29902	MBE	*Staphylococcus*	Eradicated	VB_3	Unknown		
		Streptococcus	Relapse	VB_3	Unknown		
29903	mITT	*Escherichia coli*	Pr. Rlps	EPS	Susceptible	≤0.5	
		Citrobacter braakii	Pr. Rlps	EPS	Susceptible	≤0.5	
		S. epidermidis	Pr. Rlps	VB_3	Susceptible	≤0.5	
46908	MBE	*Enterococcus faecalis*	Pr. Rlps	EPS	Susceptible	1	
50902	MBE	*S. epidermidis*	Pr. Rlps	EPS	Susceptible	1	
50909	MBE	Staph coag-neg	Pr. Rlps	EPS	Susceptible	≤0.5	
		S. epidermidis	Pr. Rlps	EPS	Susceptible	≤0.5	
		Enterococcus faecalis	Pr. Rlps	EPS	Susceptible	≤0.5	
51909	MBE	*S. haemolyticus*	Pr. Rlps	EPS	Susceptible	≤0.5	
		Streptococcus	Pr. Rlps	VB_3	Susceptible	0.5	
		S. agalactiae	Pr. Rlps	EPS	Intermediate		20
		S. agalactiae	Pr. Rlps	VB_3	Susceptible	0.38	
		Streptococcus mitis	Pr. Rlps	EPS	Susceptible	0.5	
68901	mITT	*S. epidermidis*	Pr. Rlps	EPS	Susceptible	≤0.5	
		Enterococcus faecalis	Pr. Rlps	EPS	Susceptible	1	
75902	MBE	*S. epidermidis*	Pr. Rlps	EPS	Susceptible	≤0.5	
		S. agalactiae	Pr. Rlps	EPS	Susceptible	0.5	

MBE = Microbiologically Evaluable; mITT = Modified Intent-to-Treat
Pr. Rlps = presumed relapse
EPS = Expressed prostatic secretions
VB_3 = Voided bladder 3-first 5-10 mL of urine stream immediately after prostatic massage

TABLE 21 summarizes key information, including pathogen and isolation site, for all subjects in the ITT population who acquired a superinfection. A superinfecting organism was one (other than that isolated at admission) isolated while on-therapy, up to and including the posttherapy visit. It was a culture from any site that was associated with emerging or worsening clinical signs and symptoms and/or laboratory evidence of active infection that required antimicrobial therapy.

Thirteen superinfections occurred in nine levofloxacin treated subjects; 12 superinfecting organisms were isolated from the prostate and one from urine. Fourteen superinfections occurred in 11 ciprofloxacin treated subjects; 13 superinfecting organisms were isolated from the prostate and one from both the prostate and urine.

The most common superinfecting organism was *S. haemolyticus*, which occurred more frequently in the ciprofloxacin treatment group (five subjects) than in the levofloxacin treatment group (one subject). Superinfections with *S. epidermidis* (levofloxacin, two subjects; ciprofloxacin, four subjects) and *E. faecalis* (levofloxacin, two subjects; ciprofloxacin, one subject) occurred in more than one subject in either treatment group. Other superinfecting organisms occurred in only one subject in either treatment group.

In the levofloxacin treatment group, seven pathogens in five subjects were susceptible to levofloxacin, two pathogens in two subjects were of intermediate susceptibility, and four pathogens in three subjects were resistant to levofloxacin. In the ciprofloxacin treatment group, five pathogens in four subjects were susceptible to ciprofloxacin, and nine pathogens in nine subjects were resistant to ciprofloxacin. Most resistant pathogens were *S. epidermidis* or *S. haemolyticus.*

TABLE 21
Subjects with Superinfections; Intent-to-Teat Population
(STUDY CAPSS 101)

Treatment Subject	Population	Superinfecting Organism	Site	Susceptibility	MIC (µg/mL)
Levofloxacin					
7913	MBE	*Staphylococcus epidermidis*	Prostate	Intermediate	4
		Staphylococcus warneri	Prostate	Resistant	≥8
		Enterococcus faecalis	Prostate	Resistant	≥8
7941	MBE	*Staphylococcus sciuri*	Prostate	Susceptible	≤1
		Streptococcus uberis	Prostate	Susceptible	0.5
8902	mITT	*Streptococcus agalactiae*	Prostate	Susceptible	≤1
39903	MBE	*Staphylococcus hominis*	Prostate	Intermediate	4
44902	Safety	*Enterococcus faecalis*	Prostate	Susceptible	≤1
46904	MBE	*Flavimonas oryzihabitans*	Prostate	Susceptible	≤1
		Enterobacter cloacae	Prostate	Susceptible	≤1
46923	MBE	*Streptococcus mitis*	Urine	Susceptible	0.38
94903	MBE	*Staphylococcus haemolyticus*	Prostate	Resistant	≥8
101910	MBE	*Staphylococcus epidermidis*	Prostate	Resistant	≥8
Ciprofloxacin					
29906	MBE	*Enterococcus faecalis*	Prostate	Susceptible	1
32905	MBE	*Staphylococcus haemolyticus*	Prostate	Resistant	≥4
46902	MBE	*Staphylococcus haemolyticus*	Prostate	Resistant	≥4
46903	MBE	*Staphylococcus haemolyticus*	Prostate/urine	Resistant	≥4
46931	MBE	*Staphylococcus epidermidis*	Prostate	Resistant	≥4
51913	MBE	*Staphylococcus haemolyticus*	Prostate	Resistant	≥4
60903	MBE	*Staphylococcus* coagulase-negative	Prostate	Resistant	≥4
62904	MBE	*Staphylococcus haemolyticus*	Prostate	Susceptible	1
62913	MBE	*Staphylococcus epidermidis*	Prostate	Resistant	≥4
		Streptococcus mitis	Prostate	Susceptible	1
62931	MBE	*Staphylococcus epidermidis*	Prostate	Resistant	≥4
89901	Safety	*Staphylococcus epidermidis*	Prostate	Resistant	≥4
		Streptococcus milleri	Prostate	Susceptible	0.38
		Streptococcus uberis	Prostate	Susceptible	0.50

MBE = Microbiologically Evaluable; mITT = Modified Intent-to-Treat

New infections were reported in a total of seven subjects; five were isolated in four subjects in the levofloxacin treatment group and three were isolated in three subjects in the ciprofloxacin treatment group. A new infector was a pathogen not present at admission but isolated from a VB_2, VB_3, or EPS specimen between posttherapy and poststudy. A reinfector was identified in seven subjects, six in the levofloxacin treatment group and one in the ciprofloxacin treatment group. A reinfecting organism was the re-emergence of the original organism isolated at admission in a subject with documented or presumed eradication at the posttherapy visit. Re-infecting organisms were isolated from a VB_3 or EPS specimen obtained after the posttherapy visit and associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection requiring antibacterial therapy. Both a new infector and a reinfector were identified in two subjects, one in the levofloxacin treatment group (90903) and one in the ciprofloxacin treatment group (29902). TABLE 22 summarizes information about new infections and reinfections.

In the levofloxacin treatment group, eight infecting organisms in seven subjects were susceptible to levofloxacin (MICs ≤1 µg/mL; one *Staphylococcus lentus* had a MIC = 2 µg/mL). One *Staphylococcus simulans* and one *Staphylococcus epidermidis* were resistant (MIC ≥ 8 µg/ml). In the ciprofloxacin treatment group, two infecting organisms were susceptible to ciprofloxacin in two subjects. One *Streptococcus* (unspeciated) was resistant (disk 15 mm) and one *Streptococcus* (unspeciated) was of unknown susceptibility (see TABLE 22).

TABLE 22
Subjects with New Infection and/or Reinfection: Intent-to-Treat Population
(Study CAPSS 101)

Treatment Subject	Population	Infecting Organism	NI/RI[a]	Susceptibility	MIC (µg/mL)	Disk (mm)
Levofloxacin						
17907	MBE	*Staphylococcus simulans*	New Infector	Resistant	≥8	
30902	MBE	*Staphylococcus epidermidis*	New Infector	Susceptible	≤1	
32901	mITT	*Streptococcus agalactiae*	Reinfector	Susceptible	≤1	
62928	mITT	*Enterococcus faecalis*	Reinfector	Susceptible	≤1	
84909	mITT	*Staphylococcus lentus*	New Infector	Susceptible	2	
		Leuconostoc	New Infector	Unknown		
90903	MBE	*Staphylococcus sciuri*	New Infector	Susceptible	≤1	
		Enterococcus faecalis	Reinfector	Susceptible	≤1	
94907	MBE	*Streptococcus agalactiae*	Reinfector	Susceptible	≤1	
101901	MBE	*Staphylococcus haemolyticus*	Reinfector	Susceptible	≤1	
108901	MBE	*Staphylococcus epidermidis*	Reinfector	Resistant	≥8	
Ciprofloxacin						
29902	MBE	*Streptococcus*	New Infector	Resistant		15
		Streptococcus bovis	Reinfector	Susceptible		21
606901	MBE	*Streptococcus*	New Infector	Unknown		
106903	MBE	*Enterococcus faecalis*	New Infector	Susceptible	≤0.5	

[a] NI = New Infection; RI = Reinfector
MBE = Microbiologically Evaluable; mITT = Modified Intent-to-Treat

LABELING

The only change proposed for the Microbiology subsection of the label is the addition of *Staphylococcus epidermidis.*

staphylococcus epidermidis and

If the Medical Officer finds that the indication of chronic bacterial prostatitis should be approved with these four organisms included this change is acceptable. Since the clinical trial did not determine the methicillin susceptibility of staphylococci, it can not be determined if levofloxacin is effective against methicillin-resistant staphylococci in this indication. *In vitro* data indicate that levofloxacin MIC values are above the susceptible breakpoint for many methicillin-resistant staphylococci. *Staphylococcus epidermidis* and should, therefore, be listed as *Staphylococcus epidermidis* (methicillin-susceptible strains) and

If not enough evidence is presented to allow these four organisms to be placed in list #1 but an indication of chronic bacterial prostatitis is approved then *Staphylococcus epidermidis* (methicillin-susceptible strains) and

Data provided with this submission demonstrate that the median MIC_{90} value for these two organisms **are below or equal to levofloxacin's susceptible breakpoint.**

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RECOMMENDATIONS

The sponsor should be notified of the following:

1. The addition *Staphylococcus epidermidis,* s satisfactory assuming that the Medical Officer determines that enough evidence has been presented to allow an indication of chronic bacterial prostatitis due to these organisms. *Staphylococcus epidermidis* and methicillin-susceptible strains. *In vitro* data show that methicillin-resistant strains have much higher MIC values and the clinical trial did not show that methicillin-resistant strains were treated successfully. These additional species should be added in alphabetical order. If the indication is allowed but not enough data were presented for any of these species to be individually listed then *Staphylococcus epidermidis* (methicillin-susceptible strains) and *in vitro* activity). they are not allowed in list #1.

2. The following changes should be made to the Susceptibility section:

   - **The statements reading "For testing aerobic microorganisms other than** *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Streptococcus pneumoniae***" should be revised to read "For testing** *Enterobacteriaceae,* enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa*:

   - The listing of Quality Control microorganisms should be in alphabetical order.

3. The National Committee for Clinical Laboratory Standards references at the end of the label should be updated to the January 2000 versions.

The Microbiology subsection should, therefore, read as follows: Additions are double-underlined and deletions are shown with a strikeout through them.

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 (methicillin-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

As with other drugs of 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's) 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
Streptococcus (Group C/F)
Streptococcus (Group G)
Streptococcus milleri
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter baumannii
Acinetobacter lwoffi
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
Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringes

Susceptibility Tests
Dilution techniques: Quantitative methods are used to determine antimicrobial minimum 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 ~~aerobic microorganisms other than Haemophilus influenzae, Haemophilus parainfluenzae, and Streptococcus spp. including S. pneumoniae~~ *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] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results 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* species including *Streptococcus 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 concentration 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 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 concentration 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 provide the following MIC values:

Microorganism		MIC Range (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
~~*Pseudomonas aeruginosa*~~	~~ATCC 27853~~	~~0.5-4~~
~~*Staphylococcus aureus*~~	~~ATCC 29213~~	~~0.06-0.5~~
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 ~~aerobic microorganisms other than Haemophilus influenzae, Haemophilus parainfluenzae, and Streptococcus spp. including S. pneumoniae~~ *Enterobacteriaceae*, Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa*:

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

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

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

[e] This interpretive standard is applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

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

For testing *Streptococcus* species including *Streptococcus pneumoniae* [f]:

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

[f] These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood 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 that are used 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 quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-37
~~*Pseudomonas aeruginosa*~~	~~ATCC 27853~~	~~19-26~~
~~*Staphylococcus aureus*~~	~~ATCC 25923~~	~~25-30~~
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% defibrinated sheep blood and incubated in 5% CO_2.

REFERENCES

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2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests ~~Sixth~~ Seventh Edition. Approved Standard NCCLS Document M2-A~~6~~7, Vol. ~~17~~20, No. 1, NCCLS, Wayne, PA, January, ~~1997~~ 2000.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDAs # 20634/SEI-027; 20635/SEI-026
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/MRuiz
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/YKong

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/s/

Peter Dionne
10/7/02 09:31:28 AM
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Shukal signed 10/4/02--Ken signed 10/4/02

Shukal Bala
10/10/02 11:05:26 AM
MICROBIOLOGIST

Kenneth Hastings
10/10/02 11:10:50 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**20-634; SE1-027** **20-635; SE1-026**
Submission Date:	July 26, 2002
Drug Product:	Levofloxacin 500mg Tablets Levofloxacin Injection
Trade Name:	LEVAQUIN®
Sponsor:	J & J Pharmaceutical Research & Development
Submission Type:	**Efficacy Supplement – Chronic Bacterial Prostatitis**
Review Category:	1S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.

I. BACKGROUND and SUMMARY

This is a supplement to NDA 20-634 and 20-635 for the use of levofloxacin tablets and injection (LEVAQUIN®) for the treatment chronic bacterial prostatitis in men. The proposed dosage regimen is 500 mg of levofloxacin PO or IV Q 24 hours x 28 days. This regimen has already been approved for other infections in the original NDA and other supplements, and thus, has been extensively evaluated for efficacy, safety. and clinical pharmacology / pharmacokinetics.

In this supplement, the sponsor provided one clinical pharmacology study report on the penetration of levofloxacin into prostate tissue of men undergoing scheduled resection for benign prostatic hypertrophy following administration of levofloxacin (prior to the procedure). The complete review of this report is provided below in Section II.

The following conclusions may be made from this study of 20 adult males who received three consecutive 500-mg Q 24 hr doses of levofloxacin (two PO and one IV) prior to elective surgery for removal of the prostate:

- Penetration of levofloxacin into prostate tissue appeared to be extensive, as evidenced from the individual prostate / plasma levofloxacin concentration ratios (plasma concentration at the time of prostate tissue collection) ranging from ~0.6 to ~7. In addition, approximately 70% of subjects had a ratio that was 1.0 or greater.

- Simulation of prostate tissue and plasma concentrations using a Pop PK approach resulted in an estimated penetration ratio (prostate AUC / plasma AUC) of 2.96.

- The results from this study are not included in the proposed levofloxacin labeling for the indication of treatment of acute prostatitis. Thus, the reviewer has no comments.

II. REVIEW OF CLINICAL PHARMACOLOGY STUDY

Study CAPSS-034: Evaluation of the PK and Penetration of Levofloxacin into Prostatic Tissue in Subjects Who are Undergoing Scheduled Resection for BPH and Who have Reached Steady State Levels of Levofloxacin
(Study Dates: 5/13/97 – 4/28/99)

Objectives:
Evaluate prostatic tissue and plasma concentrations of levofloxacin following two 500mg oral doses and one 500 mg IV dose.

Formulations/Treatments:
Levofloxacin 500 mg Tablets (LEVAQUIN®)
Levofloxacin 500 mg IV solution for injection (LEVAQUIN®)

Subjects:
28 healthy male subjects undergoing elective transurethal prostectomy; mean (range) age 69 (47-95) years; mean (range) weight 180 (116-253) lbs.

Study Design and Methods:
Open label, randomized Phase I study conducted at three study sites in adult males undergoing elective surgery for transurethal prostectomy. Subjects were divided into four groups and were to receive three consecutive doses of levofloxacin according to the following schedule:

Group A:
Days 1 and 2 500 mg PO Levofloxacin Q24 hr
Day 3 Single dose 500 mg IV Levofloxacin; end of infusion at 0-0.5 hours prior to surgery*

Group B:
Days 1 and 2 500 mg PO Levofloxacin Q24 hr
Day 3 Single dose 500 mg IV Levofloxacin; end of infusion at 3.75-4.25 hours prior to surgery*

Group C:
Days 1 and 2 500 mg PO Levofloxacin Q24 hr
Day 3 Single dose 500 mg IV Levofloxacin; end of infusion at 7.5-8.5 hours prior to surgery*

Group D:
Days 1 and 2 500 mg PO Levofloxacin Q24 hr
Day 3 Single dose 500 mg IV Levofloxacin; end of infusion at 24 hours prior to surgery*

*Administered over 60 minutes

Day 3 PK Plasma Samples: pre-dose (0hr), end of infusion (1 hr), 1.5, 2.0, 3.75, 5.0, 6.0 hours following completion of infusion

Day 3 Prostate Tissue Samples: Approximately 3-10 grams of prostatic tissue were collected at the time of surgery and a plasma sample was also obtained at the time of prostate tissue collection.

Analytical Methods:
Plasma and prostate tissue concentrations of levofloxacin were determined using validated HPLC-UV assays. The plasma assay was validated over the linear range from **0.05 – 5.5** µg/mL (LLOQ 0.05 µg/mL).

The validation and performance of both the plasma and prostate tissue assays were acceptable.

Data Analysis:
Plasma PK parameters for levofloxacin were determined using standard noncompartmental methods. In addition, a population PK approach and a 1000-subject Monte Carlo simulation of the prostate data was employed to determine the penetration ratio of levofloxacin into prostate tissue, i.e., AUC prostate / AUC plasma.

Results:
Of the 28 subjects enrolled into the study, 22 completed. Six subjects were withdrawn; 4 because of adverse events, one for personal reasons, and one for a protocol violation. In addition, prostate tissue data was not used from 2 subjects. Thus, paired prostate tissue and plasma data was available for 20 subjects.

Since the plasma PK of levofloxacin following 500 mg PO and IV doses have been extensively studied and reported in previous sponsor submitted NDA's and IND's, the focus will be on the prostate tissue PK of levofloxacin.

Figure 1 at the end of this review shows the concentrations of levofloxacin in prostate tissue at various times after the end of the 500 mg IV infusion on Day 3. As can be

Population PK modeling employed a 3-compartment model to best describe the plasma and prostate disposition of levofloxacin. From the Pop PK modeling, the values of the PK parameters obtained for plasma were consistent with those described using standard noncompartmental methods (i.e., CL; Vd). The volume of distribution for prostate was

igure 2 at the end of this review shows the simulation plasma and prostate **tissue concentration – time profiles for levofloxacin.** *From this data, the prostate / plasma penetration ratio was determined to be*

The results from the 1000-subject Monte Carlo simulation are shown in the following table.

Levofloxacin Prostate Tissue Penetration Estimation based on Monte Carlo Simulation of 1000 Subjects

	Penetration Ratio (Prostate AUC/Plasma AUC)
Mean	**4.14**
Median	**2.08**
Standard Deviation	**6.94**
95% CI	**0.20, 19.6**

The results show a very wide range of estimated penetration of levofloxacin into prostate tissue.

Reviewer Conclusions:
The following conclusions may be made from this study of 20 adult males who received three consecutive 500-mg Q 24 hr doses of levofloxacin (two PO and one IV) prior to elective surgery for removal of the prostate:

- Penetration of levofloxacin into prostate tissue appeared to be extensive, as evidenced from the individual prostate / plasma levofloxacin concentration ratios (plasma concentration at the time of prostate tissue collection) ranging from
  n addition, approximately 70% of subjects had a ratio that was 1.0 or greater.

- Simulation of prostate tissue and plasma concentrations using a Pop PK approach resulted in an estimated penetration ratio (prostate AUC / plasma AUC) of 2.96.

Reviewer Comments:
The results from this study are not included in the proposed levofloxacin labeling for the indication of treatment of acute prostatitis. The reviewer has no comments.

Figure 1: Prostate Levofloxacin Concentrations at Varying Times After I of Levofloxacin Infusion

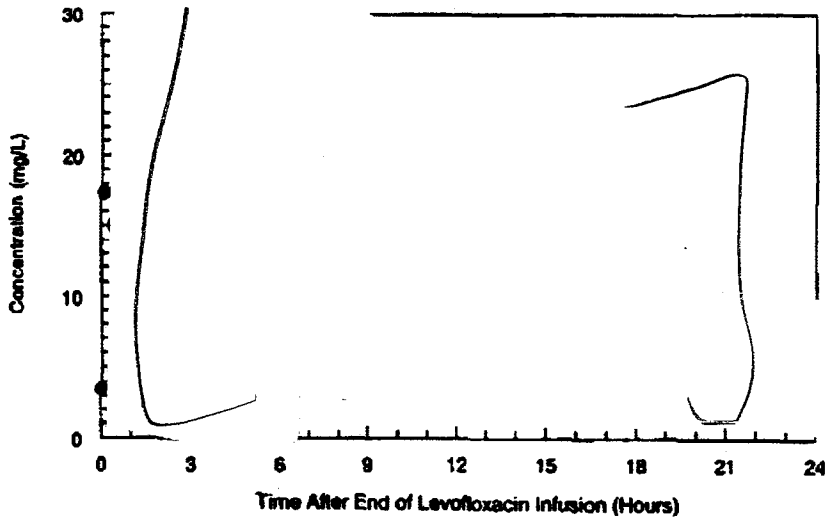
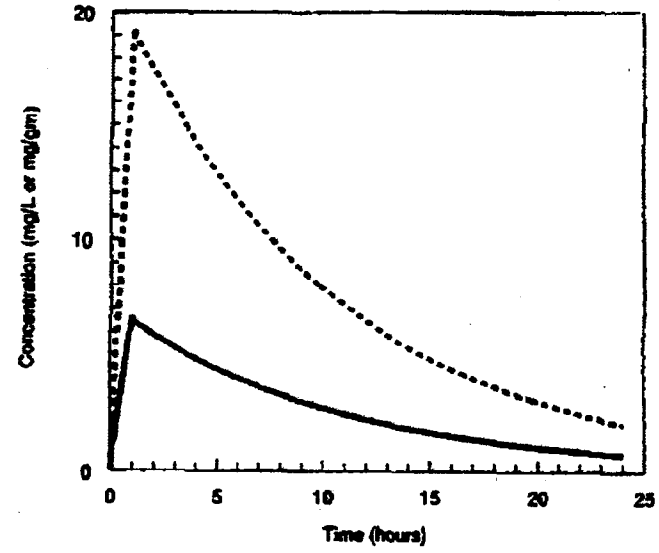


Figure 2: Simulation From the Mean Parameter Vector of the Plasma and Prostate Levofloxacin Concentration-Time Profiles



KEY: —— Plasma
- - - Prostate

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation 3

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/s/

Phil Colangelo
11/7/03 06:55:13 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-634, 20-635 SUPPL # S-027,S-026

Trade Name LEVAQUIN® Generic Name levofloxacin

Applicant Name Johnson & Johnson Pharmaceutical Research and Development HFD-590

Approval Date May 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.)? SE1

   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 /___/

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-101

Investigation #2, Study #

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 /___/

   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 /___/

   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-101

Investigation #_, Study #

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 # _ YES /_ __/ ! 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
5/23/03 02:06:02 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 20-634, 20-635 Supplement Type (e.g. SE5): SE1 Supplement Number: 027, 026

Stamp Date: July 26, 2002 Action Date: May 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.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Bacterial Prostatitis

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____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
X 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._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	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**
- ☐ **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}

_____
Regulatory Project Manager

cc: NDA 20-634/S-027, NDA 20-635/S-026
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

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

/s/

Susan Peacock
5/23/03 11:18:37 AM