CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

MICROBIOLOGY REVIEW(S)

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MICROBIOLOGY REVIEW

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

NDA #: 20-634/SEI-004

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	04-JUN-98
CDER DATE:	04-JUN-98
REVIEW ASSIGN DATE:	23-JUN-98
REVIEW COMPLETE DATE:	22-JUL-98

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SUBMISSION REVIEWED:
Supplement SEI-004 contains information to support a new indication of uncomplicated urinary tract infections

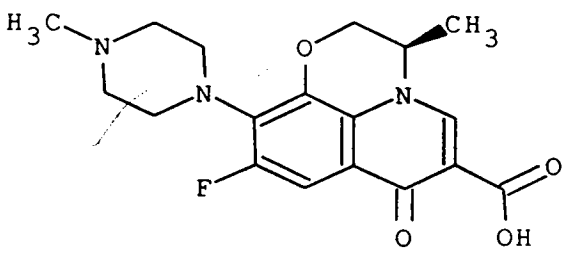
DRUG CATEGORY:
Antimicrobial: Fluoroquinolone

INDICATIONS:
Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, (requesting uncomplicated UTI)

DOSAGE FORM:
levofloxacin tablets 250 and 500 mg/tablet

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Tablets
NONPROPRIETARY/USAN: Levofloxacin tablets
CODE:
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:

This supplement provides for revisions to the Microbiology, Indications and Usage, and Dosage and Administration sections of the LEVAQUIN Tablet package insert to support a new indication for uncomplicated urinary tract infections.

The only changes proposed for the microbiology section are the movement of *Staphylococcus saprophyticus* from the *in vitro* activity listing to the *in vitro* and clinical infections listing and the addition of "Group A" after *Streptococcus pyogenes* and "Group B" after *Streptococcus agalactiae*.

The agency no longer uses the designation of "Group A" after a listing of *S. pyogenes* since this species is well recognized as belonging to this group. The designation of "Group B" after a listing of *S. agalactiae* has also recently been eliminated.

The movement of *Staphylococcus saprophyticus* into the clinical efficacy listing will depend on the approval of this organism for the indication of uncomplicated urinary tract infections.

CONCLUSIONS & RECOMMENDATIONS:

This NDA supplemental application requests approval for uncomplicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*.

The supplement is approvable from the microbiological viewpoint under section 505(b) of the Act, but the organisms allowed in the indication will have to be determined by the Medical Officer reviewing this supplement. Only *Escherichia coli* was isolated from subjects fully evaluable for microbiological efficacy in numbers greater than five to eleven isolates. The Medical Officer will have to determine if enough isolates, other than *E. coli*, were present to allow them in the indication of uncomplicated UTI.

If the above indication is approved for *Staphylococcus saprophyticus* then this organism may be moved from the *in vitro* activity only listing to the listing with clinical efficacy in the microbiology section of the label.

The addition of "Group A" after *Streptococcus pyogenes* and "Group B" after *Streptococcus agalactiae* should not be allowed. The agency no longer uses the designation of "Group A" after a listing of *S. pyogenes* since this species is well recognized as belonging to this group. The designation of "Group B" after a listing of *S. agalactiae* has also recently been eliminated.

The sponsor should be notified of the comments on page 23 of this review.

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INTRODUCTION

This supplemental application contains information in support of a request to change the labeling for levofloxacin to include an indication of uncomplicated urinary tract infections. Specific organisms for which coverage is being requested are: *Enterococcus faecalis, Staphylococcus saprophyticus, Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis.* New *in vitro* activity information has been included. This new information is derived from a literature search of levofloxacin susceptibility data related to the five targeted organisms, as well as the susceptibility data derived from the multicenter Phase III safety and efficacy study. Study LOFBO-UTI-060 which was performed to support an indication of uncomplicated urinary tract infections is the subject of this supplement. Comparisons between the activities of levofloxacin and ofloxacin and/or ciprofloxacin are usually given. The new data for the five target organisms were integrated with the susceptibility data presented in the original NDA 20-634, submitted December 21, 1995.

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

Like other quinolones, levofloxacin inhibits the activity of the Gyr A subunit of topoisomerase II and topoisomerase IV. This submission contains one reference that reports on the inhibitory activities of quinolones against DNA gyrase and topoisomerase IV purified from *Staphylococcus aureus* (1). In this study ParC and ParE proteins of topoisomerase IV encoded by genes, with or without mutations, were purified from *S. aureus.* The enzymes showed ATP-dependent decatenation and relaxing activities but had no supercoiling activity. The 50% inhibitory concentrations (IC_{50}s) for this decatenation and relaxing activity correlated with the MICs of the fluoroquinolones that were tested. These IC_{50}s for the fluoroquinolones tested were 2 to 20 times lower than IC_{50}s for supercoiling activity. These results suggest that the primary target of quinolones is topoisomerase IV in quinolone-susceptible strains of *S. aureus.* The inhibitory activities of quinolones against the topoisomerase IV from genes with a single mutation were _____ than those against the nonaltered enzyme. This suggests that mutations in the genes for topoisomerase IV confer quinolone resistance.

Levofloxacin is highly specific for bacterial topoisomerase II and IV and exhibits a large difference in selectivity between these bacterial enzymes and their eukaryotic counterparts.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

(FIVE PATHOGENS INVOLVED IN THIS SUPPLEMENT)

Susceptibility data presented in the original NDA 20-634 are shown in TABLE 1 for the five pathogens associated with uncomplicated urinary tract infections which the sponsor has requested to include in the label. These pathogens are *Enterococcus faecalis*, *Staphylococcus saprophyticus*, *Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis*. For the two gram-positive organisms median MIC_{90} values were <2.0 µg/mL, the breakpoint for susceptibility to levofloxacin. For the three gram-negative bacteria median MIC_{90} values were ≤ 0.25 µg/mL. All isolates of *Staphylococcus saprophyticus* (only 28 tested) and *Proteus mirabilis* were susceptible to levofloxacin.

TABLE 1
Activity Against UTI Organisms (Summary data from Original NDA)[a]

Organism	No. of Isolates in NDA	Compound	MIC Range (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)
Enterococcus faecalis	1540	Levofloxacin			1.56
	1441	Ofloxacin			4.0
	1431	Ciprofloxacin			1.56
Staphylococcus saprophyticus	28	Levofloxacin			0.78
	28	Ofloxacin			1.56
	28	Ciprofloxacin			0.78
Escherichia coli	5647	Levofloxacin			0.10
	5417	Ofloxacin			0.19
	5257	Ciprofloxacin			0.05
Klebsiella pneumoniae	2369	Levofloxacin			0.25
	2267	Ofloxacin			0.25
	2250	Ciprofloxacin			0.12
Proteus mirabilis	1058	Levofloxacin			0.19
	1047	Ofloxacin			0.39
	918	Ciprofloxacin			0.06

[a] Data included from 1989-1995

A literature search was conducted to identify publications from 1996 to 1997 reporting susceptibility data for levofloxacin when tested against any of the five target organisms. This was done to determine if the susceptibility pattern for these organisms had changed since the submission of the original NDA. TABLE 2 shows the data from this literature search. As seen in TABLE 2 data from 1996-1997 supported the previous observations (TABLE 1) with a few exceptions. In the new studies all isolates of *Staphylococcus saprophyticus* were susceptible to levofloxacin ($MIC_{90} \leq 0.5$ μg/mL), but only a small number were tested. All levofloxacin MIC_{90} values for the five organisms were in the susceptible range, with the exception of some collections of organisms that contained specific resistance mechanisms and two sets of *Enterococcus faecalis* isolates. One set of *E. faecalis* organisms included respiratory isolates from patients in intensive care units where ciprofloxacin was used often. In this study 81% of the isolates were susceptible to levofloxacin. The other collection of *E. faecalis* with elevated levofloxacin MICs included selected populations that were either high level gentamicin-resistant or VanB-type vancomycin-resistant. The MIC_{90} values for *E. faecalis* were at or just below the susceptible breakpoint in all studies even the ones that did not include selected populations. A set of Japanese *Klebsiella pneumoniae* clinical isolates, selected on the basis of mutations in GyrA and ParC, also had a MIC_{90} value in the resistant range. One other study with fifty isolates tested had a MIC_{90} at the susceptible breakpoint, but another study with a much greater number of isolates (2326) had a MIC_{90} of ≤ 0.5 μg/mL. The VanA-type vancomycin-resistant enterococci and β-lactamase-producing, high level gentamicin-resistant *E. faecalis* isolates were susceptible to levofloxacin.

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ON ORIGINAL

TABLE 2
Activity Against UTI Organisms (Literature Data 1996-1997)

Organism	No. of Isolates	Compound	MIC Range (µg/mL)	MIC_{90} (µg/mL)	Reference
Enterococcus faecalis	20	Levofloxacin		2.0	2
	20	Ofloxacin		4.0	2
	20	Ciprofloxacin		2.0	2
	30	Levofloxacin		1.56	3
	30	Ciprofloxacin		3.13	3
	47	Levofloxacin		>32	4
	47	Ofloxacin		>32	4
	47	Ciprofloxacin		>32	4
	1005	Levofloxacin		>16	5
	1005	Ofloxacin		>4	5
	1005	Ciprofloxacin		>2	5
Enterococcus faecalis (HLGR)[a]	20	Levofloxacin		32	2
	20	Ofloxacin		64	2
	20	Ciprofloxacin		64	2
Enterococcus faecalis (HLGR, BLA+)[a,b]	10	Levofloxacin		1.0	2
	10	Ofloxacin		2.0	2
	10	Ciprofloxacin		2.0	2
Enterococcus faecalis (VanA)	10	Levofloxacin		2.0	2
	10	Ofloxacin		2.0	2
	10	Ciprofloxacin		2.0	2
Enterococcus faecalis (VanB)	20	Levofloxacin		32	2
	20	Ofloxacin		64	2
	20	Ciprofloxacin		64	2
Staphylococcus saprophyticus	18	Levofloxacin		≤0.5	5
	18	Ofloxacin		≤2.0	5
	18	Ciprofloxacin		1.0	5
Escherichia coli	42	Levofloxacin		0.10	3
	42	Ciprofloxacin		0.05	3
	2326	Levofloxacin		≤0.50	5
	2326	Ofloxacin		≤2.0	5
	2326	Ciprofloxacin		≤0.50	5
Klebsiella pneumoniae	50	Levofloxacin		2.0	4
	50	Ofloxacin		4.0	4
	50	Ciprofloxacin		2.0	4
	44	Levofloxacin		0.20	3
	44	Ciprofloxacin		0.10	3
	26[c]	Levofloxacin		50	6
	26[c]	Ciprofloxacin		50	6
	745	Levofloxacin		≤0.50	5
	745	Ofloxacin		≤2.0	5
	745	Ciprofloxacin		≤0.50	5
Proteus mirabilis	40	Levofloxacin		0.20	3
	40	Ciprofloxacin		0.20	3
	445	Levofloxacin		≤0.50	5
	445	Ofloxacin		≤2.0	5
	445	Ciprofloxacin		≤0.50	5

[a] High level gentamicin-resistant
[b] β-lactamase-producing [c] Selected to include organisms with amino acid alterations in GyrA and ParC

Susceptibility data generated for the five targeted organisms from the Phase III study, LOFBO-UTI-060, included in this submission are presented in TABLE 3. All isolates were susceptible to levofloxacin, although some *Enterococcus faecalis* isolates had a MIC of 2.0 μg/mL which is the susceptible breakpoint and the MIC_{90} value was also at this breakpoint.

TABLE 3
Activity Against Clinical Isolates from Study LOFBO-UTI-060

Organism	No. of Isolates	Compound	MIC Range (μg/mL)	MIC_{90} (μg/mL)
Enterococcus faecalis	14	Levofloxacin		2.0
	14	Ofloxacin		4.0
Staphylococcus saprophyticus	14	Levofloxacin		0.5
	14	Ofloxacin		1.0
Escherichia coli	271	Levofloxacin		0.06
	271	Ofloxacin		≤0.125
Klebsiella pneumoniae	19	Levofloxacin		0.25
	19	Ofloxacin		0.25
Proteus mirabilis	22	Levofloxacin		0.125
	22	Ofloxacin		≤0.125

All susceptibility data were then compiled into TABLE 4 to compare the susceptibility data for the isolates from the clinical trial (LOFBO-UTI-060) with all the isolates from the literature and company studies. Only studies in which at least ten isolates were evaluated were included in the TABLE. For *Enterococcus faecalis* the median levofloxacin MIC_{90} of 2.0 μg/mL from the compiled data in TABLE 4 is equal to the MIC_{90} against the clinical trial isolates and equivalent to the value originally reported in the NDA 20-364 submission (median MIC_{90} = 1.56 μg/mL). For *Staphylococcus saprophyticus* the median levofloxacin MIC_{90} value of 0.50 μg/mL for the compiled data was identical to that observed during the clinical trial, and was slightly lower than the MIC_{90} value of 0.78 μg/mL reported in the original NDA 20-634 submission.

Escherichia coli had levofloxacin MIC_{90} values of 0.10 μg/mL and ≤ 0.10 μg/mL for the NDA 20-634 data (TABLE 1) and the compiled data (TABLE 4), respectively. The MIC_{90} value for levofloxacin was 0.06 μg/mL against the isolates from the clinical trial. Identical (median) MIC_{90} values of 0.25 μg/mL were seen for all three sets of data for *Klebsiella pneumoniae*. For *Proteus mirabilis* the levofloxacin MIC_{90} value of 0.125 μg/mL against the clinical trial isolates was slightly lower than the median MIC_{90} of 0.19 μg/mL for the compiled data and 0.20 μg/mL for the original NDA 20-634 data.

TABLE 4
Activity Against UTI Organisms (All Data)[a]

Organism	Compound	No. of Isolates	MIC Range (µg/mL) for All Isolates	No. of Data Sets[b] Reporting MIC_{90}	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)
Enterococcus faecalis	Levofloxacin	1711		33		2.0
	Ofloxacin	1582		28		4.0
	Ciprofloxacin	1588		28		2.0
Staphylococcus saprophyticus	Levofloxacin	60		4		0.5
	Ofloxacin	60		4		1.0
	Ciprofloxacin	46		3		0.78
Escherichia coli	Levofloxacin	5960		30		≤0.10
	Ofloxacin	5688		26		≤0.125
	Ciprofloxacin	5289		24		0.050
Klebsiella pneumoniae	Levofloxacin	2508		32		0.25
	Ofloxacin	2336		27		0.25
	Ciprofloxacin	2370		26		0.12
Proteus mirabilis	Levofloxacin	1120		23		0.19
	Ofloxacin	1069		21		0.20
	Ciprofloxacin	958		20		0.06

[a] Data compiled from references in TABLES 1 and 2 and from LOFBO-UTI-060 study (TABLE 3)
[b] Only data sets including at least 10 organisms were included in MIC_{90} evaluation

In general levofloxacin had MICs half those seen for ofloxacin. Against the gram-positive bacteria levofloxacin and ciprofloxacin had comparable MICs. The breakpoint for susceptibility for ciprofloxacin is 1.0 µg/mL compared to a susceptibility breakpoint of 2.0 µg/mL for levofloxacin. Therefore, the median MIC_{90} for levofloxacin against *Enterococcus faecalis* is in the susceptible range, but is in the intermediate range for ciprofloxacin. Median MIC_{90} values for all three fluoroquinolones tested against *Staphylococcus saprophyticus* were in the susceptible range. Against gram-negative bacteria levofloxacin had MICs equivalent to, or one or two dilutions higher than, ciprofloxacin. There appear to be no significant changes in susceptibility profiles over time for the tested quinolones against the targeted organisms. The only targeted pathogen that has a MIC_{90} close to the susceptible breakpoint is *Enterococcus faecalis*. The MIC_{90} value was the same in the original NDA and this organism is in the label under complicated urinary tract infections.

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

No new information is included in this submission. It is well known that fluoroquinolone MICs are not significantly affected by changes in culture media, human serum or a CO_2 atmosphere. Use of very heavy inocula (100 x normal) may cause a slight (usually only two-fold) increase in MIC value. The only factors that normally result in significant decreases in activity are a reduction in pH of the culture medium from 7.0 to 6.0 or lower and excessively high concentrations of magnesium (9mM) and calcium (50 mM) ions. The decrease in activity at low pH could come into play in urinary tract infections. Human urine has a pH around 5 to 6. This could be significant since *Enterococcus faecalis* has an *in vitro* MIC_{90} of 2.0 µg/mL which is the susceptible breakpoint. The concentration of levofloxacin in the urine over a 36 hour post-dose period ranged from 17 to 110 µg/mL, however, so a decrease in activity may not make a difference.

BACTERICIDAL ACTIVITY

No new information is included in this submission. All of the fluoroquinolones show bactericidal activity.

MECHANISMS OF RESISTANCE STUDIES

The frequency of spontaneous mutation *in vitro* ranges from 10^{-9} to 10^{-10} for most species. For most fluoroquinolones resistance frequency rates are higher for *Pseudomonas aeruginosa* at approximately 10^{-7}.

Studies have shown that quinolones inhibit DNA gyrase and DNA topoisomerase IV. Both enzymes act by a double strand DNA break mechanism and are essential for bacterial growth. These enzymes cooperate in DNA replication to facilitate DNA unlinking and chromosome segregation. Gyrase, an A_2B_2 tetramer encoded by the *gyrA* and *gyrB* genes, catalyses negative DNA supercoiling and is thought to act ahead of the replication fork neutralizing positive supercoils arising from DNA unwinding. Topoisomerase IV is a C_2D_2 complex specified by *parC* and *parE* genes that functions to allow segregation of daughter chromosomes during cell division. Point mutations in discrete regions of the gyrase and topoisomerase IV genes; the quinolone resistance-determining regions (QRDRs); are responsible for the development of resistance. For most fluoroquinolones resistance in gram-positive organisms arises through mutation of the *parC* or *parE* genes which precedes changes in gyrase genes. In gram-negative bacteria, gyrase is usually the prime target. This submission contains one study (1) that evaluated the inhibitory activities of quinolones against DNA gyrase and topoisomerase IV purified from *Staphylococcus aureus*. This study showed that the inhibitory activities of fluoroquinolones against the decatenation activity of topoisomerase IV were higher than those against the supercoiling activity of DNA gyrase. The ratio (IC_{50} for DNA gyrase/IC_{50} topoisomerase IV) for enzymes from *S. aureus* varied from 1.7 to 20.8.

Sparfloxacin had one of the lowest ratios, which may indicate less preference for topoisomerase IV. In *Escherichia coli* the IC_{50} values for most fluoroquinolones are lower for DNA gyrase supercoiling than for decatenation. The main target in gram-negative bacteria appears to be gyrase. In this study the inhibitory activities of quinolones against topoisomerase IV which contained a single amino acid change were from eight to 95 times weaker than those against nonaltered enzyme. The inhibitory activity for double mutants was usually much lower than for the single-mutants. These results suggest that mutations in DNA gyrase and/or topoisomerase IV genes confer quinolone resistance.

Some fluoroquinolones are also substrates for efflux pumps, such as NorA in *Staphylococcus aureus*. These pumps can cause bacteria to become resistant to certain fluoroquinolones by pumping the drug out of the cell. Levofloxacin is a substrate for this mechanism. Some gram-negative bacteria may become resistant to fluoroquinolones and many other types of antimicrobials by changes in porins that alter the uptake of drugs.

Plasmid mediated resistance was unknown until recently when it was identified in *Klebsiella pneumoniae*. This submission includes a study on this plasmid (7). In this paper a multiresistance plasmid from a clinical isolated of *Klebsiella pneumoniae* increased quinolone resistance to MICs as high as 32 μg/mL for ciprofloxacin when transferred to strains of *K. pneumoniae* deficient in outer-membrane porins. Much lower resistance was seen when this plasmid was introduced into *K. pneumoniae* or *E. coli* strains with normal porins. The plasmid generally increased quinolone resistance from eight-fold to 64-fold but because MICs in the parent were initially very low, MICs in the plasmid containing recipients were usually still susceptible if the drug could get into the cell. The plasmid had a wide host range and expressed quinolone resistance in other enterobacteriaceae and in *Pseudomonas aeruginosa*. A plasmid containing strain that was still susceptible to ciprofloxacin produced quinolone-resistant mutants at a frequency 100 times the frequency seen with a plasmid-free strain. The plasmid did not have a general mutator effect since the frequency of resistance to rifampin and some other compounds was not changed. The plasmid confers broad resistance to multiple antibiotics. The same plasmid was detected in two other clinical strains of *Klebsiella pneumoniae* and one strain of *Escherichia coli*. The mechanism of this resistance is not known. Attempts to show decreased quinolone accumulation or drug inactivation have been uninformative. Provision of a quinolone-resistant DNA gyrase or DNA topoisomerase IV is unlikely, given the usual dominance of susceptible alleles over resistant ones. Protection of a quinolone target or improved repair of quinolone-induced damage has not been explored.

Mutations that cause one fluoroquinolone to have higher MICs will also confer higher MICs to other fluoroquinolones. Some fluoroquinolones may have much lower MICs against the parent strain than others, however, so a mutant that is resistant to one fluoroquinolone may still be susceptible to another although both drugs will have higher MIC values. The MIC value may also increase more for one fluoroquinolone than for another against the same species.

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RESISTANCE DEVELOPMENT DURING THERAPY

During the clinical trial (LOFBO-UTI-060) susceptibility tests were performed on pathogens isolated at baseline and during post-treatment evaluations. Two hundred and four pathogens were isolated at admission in the levofloxacin treatment group, 203 had susceptibility results. All were susceptible to levofloxacin except for one resistant *Staphylococcus aureus* isolate that was resistant to both levofloxacin and ofloxacin. Two hundred pathogens were isolated in the ofloxacin treatment group, of which 196 had susceptibility results. Two isolates had intermediate susceptibility to ofloxacin.

In the levofloxacin treated group there were 15 isolates that persisted at the post-therapy visit. None of these isolates had more than a 2-fold increase in MIC (within the error of the assay) for either levofloxacin or ofloxacin. In the ofloxacin treated group there were 11 isolates that persisted at the post-therapy visit. Two *Escherichia coli* isolates had increases in MICs of more than one dilution during treatment. An isolate from patient 8012 went from a levofloxacin MIC of 0.03 μg/mL to 0.5 μg/mL (16-fold increase); the ofloxacin MIC increased from ≤ 0.125 μg/mL to 1 μg/mL (8-fold increase). An *E. coli* isolate from patient 15031 had a levofloxacin MIC of 0.03 μg/mL at admission and a levofloxacin MIC of 2 μg/mL post-therapy (64-fold increase). This isolate's ofloxacin MIC went from ≤ 0.125 μg/mL to 2 μg/mL (16-fold increase). At the last post-therapy visit the MIC values were 0.06 μg/mL for levofloxacin and ≤ 0.125 μg/mL for ofloxacin (basically the same as at admission). No definitive testing was done to confirm that the post-treatment and pretreatment isolates were the same. It appears that treatment does not cause increases in MIC values.

PRECLINICAL EFFICACY (*IN VIVO*)

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PHARMACOKINETICS/BIOAVALIBILITY

Most of the pharmacokinetic information is referenced to the original NDA 20-634.

Levofloxacin is completely and rapidly absorbed and distributed after oral administration. Absolute oral availability is about 99%. Peak plasma levels are approximately 5 μg/mL after a single 500-mg dose and slightly higher at steady-state. Peak levels occur 1-2 hours after oral administration. The amount absorbed increases linearly with an oral dose in the 50 to 1000 mg range. Administration with meals slightly delays absorption but has little or no effect on the peak plasma levels and total absorption.

Levofloxacin is minimally metabolized to levofloxacin N-oxide and desmethyl-levofloxacin. These metabolites account for less than 5% of the dose.

The excretion of levofloxacin is primarily by renal elimination with approximately 60-80% of a dose eliminated unchanged in the urine within 48 hours of administration. Protein binding to serum albumin is approximately_____ over a range of levofloxacin concentrations from_____.

This supplement contains information on an open-label, randomized, two-way crossover study comparing the bioavailability of levofloxacin from two 125-mg clinical tablets and a 250-mg tablet in healthy male volunteers (Study LOFBO-PHI0-096). Urine was collected from 0-12 hours, 12-24 hours, and 24-36 hours after dosing. The concentration of levofloxacin in the urine was determined for each collection period. The results are presented in TABLE 5.

TABLE 5
Mean ± SD Concentrations of Levofloxacin in the Urine of Healthy Volunteers after a 250-mg Oral Dose of Levofloxacin[a]

Collection Interval	Concentration in Urine (μg/mL) (Treatment A)	(Treatment B)
0-12 hours	110 ± 32	108 ± 31
12-24 hours	77 ± 30	63 ± 22
24-36 hours	19 ± 8	17 ± 7
N[b]	15	16

[a] Administered as two 125-mg clinical tablets in Treatment A and one 250-mg marketed-image tablet in Treatment B.
[b] Of the 16 enrolled subjects, one subject withdrew from the study after completion of one study period (market-image tablet) due to an upper respiratory tract infection.

The above table demonstrates that during the 36-hour post-dose period, mean concentrations of levofloxacin achieved in the urine ranged _____. This is several times greater than the MIC_{90} values of the pathogens commonly associated with uncomplicated UTI (MIC_{90} values range _____ for these pathogens).

EXPERIMENTAL ANIMAL INFECTION STUDIES

No new information or studies were included in this submission. Studies included in the original NDA 20-634 showed that given orally, levofloxacin was equivalent to ciprofloxacin in protecting mice with experimental systemic infections induced by the gram-negative bacteria *Escherichia coli*. Levofloxacin was 2-times more potent or equipotent to ciprofloxacin in treating *Klebsiella pneumoniae* systemic infections. Levofloxacin, given orally, was significantly more potent than ciprofloxacin and ofloxacin in protecting mice from experimental systemic infections induced by methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*.

In an experimental murine model of pyelonephritis oral levofloxacin was equipotent to ciprofloxacin in reducing the viable number of *Proteus mirabilis* from the kidneys of infected rats. Levofloxacin given once daily was superior to ciprofloxacin given once daily or twice a day, in reducing the viable numbers of methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* in the kidneys of infected mice.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

The sponsor has conducted one phase III study to support the proposed new indication of uncomplicated urinary tract infection (UTI). The study was conducted in the United States. Levofloxacin has been previously approved for complicated UTI. The study was a double-blind trial and used ofloxacin as a comparator. Levofloxacin was dosed at 250 mg once a day for three days. Ofloxacin was dosed at 200 mg twice daily for three days. The trial included 298 subjects (157 microbiologically evaluable) in the levofloxacin arm and 296 subjects (165 microbiologically evaluable).

An organism was considered a pathogen if it was present in urine culture at $\geq 10^5$ cfu/mL. A subset of subjects with an urine colony count of $\geq 10^3$ cfu/mL but $<10^5$ cfu/mL was also analyzed. Efficacy endpoints included microbiological eradication rates and clinical response rates by pathogen. Microbiological and clinical evaluations were made at admission and at the post-therapy visit (5-9 days after completion of study drug). For subjects with an admission pathogen and a successful clinical outcome at the post-therapy visit, microbiological and clinical evaluations were also made at a post-study (long-term) visit four to six weeks after completion of the study drug.

The microbiological response for pathogens isolated at admission was determined by categorizing the post-therapy/early withdrawal culture results as:

- **Eradicated:** Absence of the admission pathogen ($<10^3$cfu/mL) in post-therapy urine culture obtained in the absence of potentially effective antibiotics.
- **Persisted:** Continued presence of the admission pathogen in the post-therapy culture (defined as $\geq 10^3$ cfu/mL).
- **Presumed Persisted:** Presumed continued presence of the admission pathogen at post-therapy for subjects with clinical failure and one of the following: no post-therapy (test-of-cure) culture was taken; a negative ($<10^3$ cfu/mL) post-therapy culture was obtained while on potentially effective antibiotics; or, as a working definition, a negative ($<10^3$ cfu/mL) post-therapy culture was obtained on Days 1, 2, 3, or 4 after the last dose of study drug.
- **Persisted with Acquisition of Resistance:** Continued presence of the admission pathogen in the post-therapy culture ($\geq 10^3$ cfu/mL) with documented acquisition of resistance.
- **Unknown:** No post-therapy culture available, or a negative culture was obtained in the presence of potentially effective antibiotics (except as noted above for presumed persisted, and includes as a working definition, those subjects who are clinical cures or improved, exhibit post-therapy culture results of no growth, and are on potentially effective antibiotics).

The microbiological response for each admission pathogen at the post-study (long-term) follow-up visit (four to six weeks after the post-therapy visit) was based on microbiological culture data and was assessed in subjects who had clinical success at post-therapy as:

- **Eradicated:** Continued absence of the admission pathogen ($<10^3$ cfu/mL) in the post-study (long-term) urine culture. Subjects with a clinical outcome of cured or improved where pathogens persisted at post-therapy but were absent ($<10^3$ cfu/mL) in the post-study urine culture (definition developed subsequent to the protocol).
- **Persisted:** (definition developed subsequent to the protocol to account for subjects who were clinically cured at post-study but had a persistent pathogen): Continued presence of the admission pathogen in the post-study urine culture at $\geq 10^3$ cfu/mL.
- **Microbiological Relapse:** Reappearance of an organism identical to the admission pathogen and present at the same or higher colony count as isolated at admission, isolated from urine culture at the post-study visit following eradication of the original admission pathogen at the post-therapy visit.
- **Presumed Microbiological Relapse:** Presumed presence of the admission pathogen at the post-study follow-up visit for subjects who developed signs and symptoms of UTI necessitating antibiotic therapy (clinical relapse) but for whom no culture results were available prior to antibiotic treatment of the clinical relapse.
- **Unknown:** No culture results available (except as noted above for presumed microbiologic relapse) or a negative culture was obtained while on or following a course of potentially effective antibiotics administered between the post-therapy and post-study cultures (this includes the case of the presence of an asymptomatic urinary tract superinfector for which antimicrobial therapy was administered between the post-therapy and post-study visits).

MICROBIOLOGICAL ERADICATION RATES BY PATHOGEN

The microbiological eradication rates achieved at the post-therapy visit for subjects fully evaluable for microbiological efficacy in each treatment group are shown by pathogen in TABLE 6. For all admission pathogens, the overall microbiological eradication rates by pathogen in the levofloxacin and ofloxacin treatment groups were 95.8% and 93.6%, respectively. The most prevalent pathogens for both groups were gram-negative aerobes (with *Escherichia coli* being the most prevalent species by far). The microbiological eradication rates for gram-negative aerobes were comparable for both regimens (levofloxacin, 98.1% and ofloxacin, 95.8%). In contrast, for the relatively small group of gram-positive aerobes, levofloxacin treatment resulted in a higher eradication rate than ofloxacin (88.5% vs. 73.7%) due primarily to a difference in eradication rates for *Enterococcus faecalis* (90% vs. 33.3%).

TABLE 6
Microbiological Response at Post-therapy Summarized by Pathogen:
Subjects Fully Evaluable for Microbiological Efficacy

	LEVOFLOXACIN			OFLOXACIN		
Pathogen	N	Eradicated	Persisted	N	Eradicated	Persisted
Escherichia coli	127	125 (98.4)	2 (1.6)	138	131 (94.9)	7 (5.1)
Klebsiella pneumoniae	11	10 (90.9)	1 (9.1)	8	8 (100.0)	0 (0.0)
Enterococcus faecalis	10	9 (90.0)	1 (10.0)	3	1 (33.3)	2 (66.7)
Staphylococcus saprophyticus	8	8 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)
Proteus mirabilis	7	7 (100.0)	0 (0.0)	14	14 (62.5)	0 (0.0)
Streptococcus agalactiae	8	5 (62.5)	3 (37.5)	8	5 (62.5)	3(37.5)
Staphylococcus aureus	5	5 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)
Enterobacter cloacae	4	4 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Enterobacter aerogenes	2	2 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Staphylococcus saccharolyticus	2	1 (50.0)	1 (50.0)	0	0 (0.0)	0 (0.0)
Streptococcus viridans	2	2 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Citrobacter diversus	1	1 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Citrobacter freundii	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Enterobacter agglomerans	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Pseudomonas aeruginosa	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Staphylococcus wameri	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Alcaligenes faecalis	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Citrobacter amalonaticus	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Providencia stuartii	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Pseudomonas putida	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Streptococcus mutans	0	0 (0.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Total by Pathogen	191	183 (95.8)	8 (4.2)	187	175 (93.6)	12 (6.4)
Total by Subject	157	151 (96.2)	6 (3.8)	165	153 (92.7)	12 (7.3)

Note: Numbers in parentheses are percentages for that category.

The most common pathogen, *E. coli*, was eradicated by levofloxacin in 98.4% of cases, compared with a 94.9% eradication rate with ofloxacin. The next most prevalent gram-negative pathogens were *Klebsiella pneumoniae* and *Proteus mirabilis*. *Klebsiella pneumoniae* had an eradication rate of 90.9% with levofloxacin treatment compared with 100% with ofloxacin. *Proteus mirabilis* was eradicated in 100% of both levofloxacin and ofloxacin treated subjects. With the exception of *Enterococcus faecalis*, which was eradicated by levofloxacin in 90% of cases versus 33% of cases with ofloxacin treatment, the eradication rates were similar between the two treatment groups for the gram-positive pathogens *Streptococcus agalactiae, Staphylococcus saprophyticus* and *Staphylococcus aureus*. Except for *Escherichia coli*, there were only a few isolates of each of the other species (5-11 isolates). These small numbers of isolates may not be sufficient to allow them in the indication of uncomplicated urinary tract infections. All of these species, however, except for *Staphylococcus saprophyticus* are in the microbiology section's list of organisms that have clinical efficacy (due to other indications). The Medical Officer will have to decide if enough isolates have been tested to allow them into the Indications and Usage section under uncomplicated UTI.

TABLE 7 shows the eradication rates per pathogen for isolates that were possible pathogens ($\geq 10^3$ cfu/mL but $\leq 10^5$ cfu/mL).

TABLE 7
Microbiological Response at Post-therapy Summarized by Pathogen:
Subjects Possibly Evaluable for Microbiological Efficacy ($\geq 10^3$ but $\leq 10^5$ cfu/mL)

	LEVOFLOXACIN			OFLOXACIN		
Pathogen	N	Eradicated	Persisted	N	Eradicated	Persisted
Escherichia coli	42	40 (95.2)	2 (4.8)	38	36 (94.7)	2 (5.3)
Enterococcus faecalis	8	7 (87.5)	1 (12.5)	4	3 (75.0)	1 (25.0)
Streptococcus agalactiae	4	0 (0.0)	4 (100.0)	5	5 (100.0)	0 (0.0)
Staphylococcus aureus	3	3 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Staphylococcus saprophyticus	2	2 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Enterobacter aerogenes	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Klebsiella ornithinolytica	1	1 (100.0)	0 (0.0)	0	0 (00.0)	0 (0.0)
Proteus mirabilis	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Staphylococcus haemolyticus	1	1 (100.0)	0 (0.0)	0	0 (00.0)	0 (0.0)
Streptococcus bovis	1	1 (100.0)	0 (0.0)	0	0 (00.0)	0 (0.0)
Streptococcus salivarius	1	1 (100.0)	0 (0.0)	0	0 (00.0)	0 (0.0)
Citrobacter diversus	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Klebsiella oxytoca	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Klebsiella pneumoniae	0	0 (0.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Staphylococcus hominis	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Streptococcus milleri	0	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Total by Pathogen	65	58 (89.2)	7 (10.8)	57	54 (94.7)	3 (5.3)
Total by Subject	55	48 (87.3)	7 (12.7)	49	46 (93.9)	3 (6.1)

Note: Numbers in parentheses are percentages for that category

The eradication rates for these possible pathogens were similar to those presented in TABLE 6 for the fully evaluable pathogens ($\geq 10^5$ cfu/mL). The only significant difference is for *Streptococcus agalactiae*. When treated with levofloxacin all four isolates persisted and the five isolates treated with ofloxacin were eradicated. For the fully evaluable pathogens, 62.%% (5/8) of the *S. agalactiae* isolates were eradicated in both treatment groups.

SUPERINFECTION

In subjects fully evaluable for microbiological efficacy, three levofloxacin treated subjects and one ofloxacin treated subject developed superinfections with a total of eight superinfecting organisms. Four isolates had known susceptibility information; three were susceptible to both study drugs and one was resistant to both study drugs. Susceptibility to both study drugs was unknown for four isolates. TABLE 8 shows the pathogens and susceptibility information for all subjects who acquired a superinfection.

TABLE 8
Subjects with Superinfections
Subjects Fully Evaluable for Microbiological Efficacy

Subject Number	Period	Pathogen	Susceptibility	
			Levofloxacin	Ofloxacin
Levofloxacin				
4002	Post-therapy	*Escherichia coli*	Susceptible	Susceptible
	Post-therapy	*Proteus mirabilis*	Susceptible	Susceptible
	Post-therapy	*Providencia stuartii*	Susceptible	Susceptible
12019	Post-therapy	*Staphylococcus haemolyticus*	Resistant	Resistant
22014	Post-therapy	*Staphylococcus*	Unknown	Unknown
	Post-therapy	*Streptococcus*	Unknown	Unknown
	Post-therapy	*Streptococcus agalactiae*	Unknown	Unknown
Ofloxacin				
25024	Post-therapy	*Viridans streptococci*	Unknown	Unknown

MICROBIOLOGICAL RESPONSE AT LONG-TERM FOLLOW-UP

Subjects who completed the post-therapy visit with clinical success (cured or improved) were scheduled to return for a long-term (post-study) follow-up visit four to six weeks after completion of therapy. Subjects for whom an admission pathogen was eradicated at the post-therapy visit and reappeared in a culture obtained at the post-study follow-up visit were considered to have microbiological relapse. Eight (5.1%) of 157 levofloxacin treated subjects and three (1.8%) of 165 ofloxacin treated subjects had a documented microbiological relapse. The eleven subjects who relapsed are listed in TABLE 9. Four of these subjects (three in the levofloxacin group and one in the ofloxacin group) had $\geq 10^5$ cfu/mL in the post-study urine culture but had no associated clinical signs and symptoms. Three levofloxacin subjects and eleven ofloxacin subjects were presumed to have microbiological relapse based on clinical signs and symptoms of UTI necessitating antibiotic treatment but had unknown urine culture results.

TABLE 9
Subjects With a Microbiological Relapse
Subjects Fully Evaluable for Microbiological Efficacy

Subject Number	Admission Pathogen	Reinfector[a]	Post-study Susceptibility Levofloxacin	Ofloxacin	Post-study (Long-Term) Clinical Response
Levofloxacin					
4002	*Enterobacter cloacae*	____	____	____	CR/NI
7017	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*[b]	Susceptible	Susceptible	Cure
7028	*Escherichia coli*	____	____	____	CR/NI
12012	*Staphylococcus saprophyticus*	*Staphylococcus saprophyticus*	Susceptible	Susceptible	CR/NI
18005	*Escherichia coli*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
19031	*Escherichia coli*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
60010	*Streptococcus agalactiae*	____	____	____	CR/NI
60017	*Escherichia coli*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
60020	*Escherichia coli*	*Escherichia coli*[b]	Susceptible	Susceptible	Cure
62006	*Escherichia coli*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
64018	*Escherichia coli*	*Escherichia coli*[b]	Susceptible	Susceptible	Cure
Ofloxacin					
4033	*Escherichia coli* *Staphylococcus aureus*[c]	____	____	____	CR/NI
12018	*Escherichia coli*	____	____	____	CR/NI
12023	*Escherichia coli*	____	____	____	CR/NI
16013	*Escherichia coli*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
18036	*Proteus mirabilis*	____	____	____	CR/NI
19025	*Escherichia coli*	____	____	____	CR/NI
19028	*Escherichia coli*	*Escherichia coli*[b]	Susceptible	Susceptible	Cure
22018	*Escherichia coli*	____	____	____	CR/NI
23007	*Escherichia coli*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
25015	*Escherichia coli*	____	____	____	CR/NI
25029	*Escherichia coli*	____	____	____	CR/NI
60015	*Streptococcus agalactiae*	____	____	____	CR/NI
61009	*Streptococcus agalactiae*	____	____	____	CR/NI
65024	*Escherichia coli*	____	____	____	CR/NI

[a] Subjects for whom a reinfector is not noted were presumed to have microbiological relapse based on clinical signs and symptoms of UTI which necessitated antibiotic therapy.
[b] Classified as colonizers at post-study (long-term) follow-up as subject was asymptomatic but had $\geq 10^5$ cfu/mL in urine culture resulting in a microbiological response of relapse.
[c] Possible admission pathogen (i.e. $\geq 10^3$ cfu/mL but $\leq 10^5$ cfu/mL).
Note: CR/NI = Clinical Relapse/New Infection

Among subjects fully evaluable for microbiological efficacy with a post-study (long-term) clinical response of clinical relapse/new infection, new infections (i.e., an infection in which an organism other than the original admission pathogen was isolated) were seen in three levofloxacin treated subjects and one ofloxacin treated subject as shown in TABLE 10. In all cases the isolates were found to be susceptible to levofloxacin and ofloxacin.

TABLE 10
New Infector Pathogens of Subjects With Post-study (Long-Term)
Clinical Response of Clinical Relapse/New Infection

Subject Number	Admission Pathogen	New Infector Pathogen	New Infector Susceptibility		Post-study (Long-Term) Clinical Response
			Levofloxacin	Ofloxacin	
Levofloxacin					
4021	*Escherichia coli* *Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	Susceptible	Susceptible	CR/NI
18029	*Enterococcus faecalis*	*Escherichia coli*	Susceptible	Susceptible	CR/NI
23015	*Staphylococcus aureus*	*Staphylococcus saprophyticus*	Susceptible	Susceptible	CR/NI
Ofloxacin					
65035	*Klebsiella pneumoniae*	*Escherichia coli*	Susceptible	Susceptible	CR/NI

Note: CR/NI = Clinical Response/New Infection

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CLINICAL RESPONSE BY PATHOGEN

Clinical response rates for subjects fully evaluable for microbiological efficacy infected with uropathogens (number ≥ 5 in either treatment arm) alone or in combination with other pathogens are shown in TABLE 11.

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TABLE 11
Clinical Response for Subjects with Pathogen (no. ≥5)
Subjects Fully Evaluable for Microbiological Efficacy

Pathogen(s) from Urine Culture	No. (%) of Subjects							
	Levofloxacin				Ofloxacin			
	N[a]	Cured	Improved	Failed	N[a]	Cured	Improved	Failed
Escherichia coli	125	107 (85.6)	17 (13.6)	1 (0.8)	133	116 (87.2)	13 (9,8)	4 (3.0)
Klebsiella pneumoniae	11	11 (100.0)	0 (0.0)	0 (0.0)	8	8 (100.0)	0 (0.0)	0 (0.0)
Enterococcus faecalis	10	9 (90.0)	1 (10.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	0 (0.0)
Staphylococcus saprophyticus	8	7 (87.5)	0 (0.0)	1 (12.5)	3	3 (100.0)	0 (0.0)	0 (0.0)
Proteus mirabilis	7	6 (85.7)	1 (14.3)	0 (0.0)	14	14 (100.0)	0 (0.0)	0 (0.0)
Streptococcus agalactiae	8	8 (100.0)	0 (0.0)	0 (0.0)	8	6 (75.0)	1 (12.5)	1 (12.5)
Staphylococcus aureus	5	5 (100.0)	0 (0.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	0 (0.0)

[a] N= Number of subjects who had that pathogen al0ne or in combination with other pathogens.

Escherichia coli was the most prevalent pathogen across the two treatment groups. Clinical success rates (cured + improved) for this pathogen were similar across the two treatment groups (99.2% for levofloxacin and 97.0% for ofloxacin). Success rates for the less commonly seen pathogens ranged from 87.5% to 100% in the levofloxacin group with generally comparable results in the ofloxacin group.

TABLE 12 shows the clinical outcome of the 191 pathogens from patients that were fully evaluable for microbiological efficacy.

TABLE 12
Clinical Outcome for Pathogens
Subjects Fully Evaluable for Microbiological Efficacy

		Clinical Outcome		
Number of Pathogens	Microbiological Outcome	Cure	Improved	Failed
183	Eradicated	162	19	2
8	Persisted	7	0	1

One subject each whose pathogen was *Escherichia coli*, *Staphylococcus saprophyticus*, or *Staphylococcus saccharolyticus* failed. The *Escherichia coli* and *Staphylococcus saprophyticus* isolates were eradicated, only the isolate of *S. saccharolyticus* persisted.

TABLE 13 shows the clinical outcome of the 65 pathogens from patients possibly evaluable for microbiological efficacy (pathogen present at $\geq 10^3$ cfu/mL but $\leq 10^5$ cfu/mL).

TABLE 13
Clinical Outcome for Pathogens
Subjects Possibly Evaluable for Microbiological Efficacy ($\geq 10^3$ but $\leq 10^5$ cfu/mL)

		Clinical Outcome		
Number of Pathogens	Microbiological Outcome	Cure	Improved	Failed
58	Eradicated	55	2	1
7	Persisted	4	0	3

One subject each whose pathogen was *Streptococcus bovis*, or *Streptococcus agalactiae*, and two whose pathogen was *Escherichia coli* failed. The *Streptococcus bovis* isolate was eradicated and the other three pathogens persisted.

There were very few failures even among the pathogens that persisted. There was no correlation between persisting pathogens and failure in the subjects fully evaluable for microbiological efficacy. There was some correlation between persisting pathogens and failure among the patients who had possible pathogens. Almost half (3 of 7) of the persisting pathogens led to failures.

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The sponsor should be notified of the following:

1. If levofloxacin is approved for uncomplicated UTI caused by *Staphylococcus saprophyticus* then this organism may be placed in the microbiology section of the label in the listing that has both *in vitro* activity and clinical efficacy. If this occurs then the organism should be removed from the *in vitro* activity only listing.

2. The designation "Group A" after *Streptococcus pyogenes* should be deleted. The agency no longer uses the designation of "Group A" after a listing of *S. pyogenes* since this species is well recognized as belonging to this group.

3. The designation "Group B" after *Streptococcus agalactiae* should be deleted. The designation of "Group B" after a listing of *S. agalactiae* has also recently been eliminated by the Agency since this species is well recognized as belonging to this group.

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/S/

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir /S/ /S/ Signature 11/19/98 Date
HFD-590/TLMicro Signature 8/18/98 Date

CC:
HFD-590/Original NDA # 20634/SLI-004
HFD-590/Division File
HFD-590/TLMicro/SLard
HFD-590/Micro/PDionne
HFD-590/MO/RHopkins
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/RAnderson

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SEP 10 1998

MICROBIOLOGY REVIEW

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

NDA #: 20-635/SEI-003

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	04-JUN-98
CDER DATE:	04-JUN-98
REVIEW ASSIGN DATE:	22-JUN-98
REVIEW COMPLETE DATE:	22-JUL-98

SPONSOR: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

CONTACT PERSON: Wayne Napoliello
Manager, Regulatory Affairs
Phone Number: (908) 704-4879

SUBMISSION REVIEWED: Supplement SEI-003 contains information to support a new indication for uncomplicated urinary tract infections

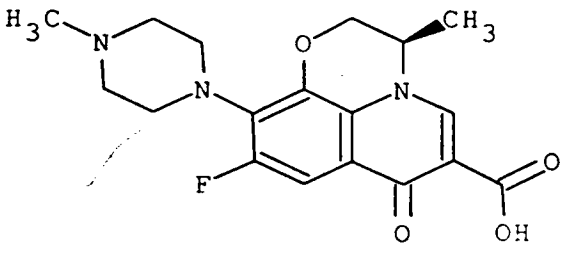
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, (requesting uncomplicated UTI)

DOSAGE FORM: levofloxacin injection 25 mg/mL, 20 mL vials

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Injection
NONPROPRIETARY/USAN: Levofloxacin injection
CODE:
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 20-634—LEVAQUIN Tablets.

BACKGROUND:

This supplement only contains proposed labeling and an environmental assessment.

The only changes proposed for the microbiology section is the movement of *Staphylococcus saprophyticus* from the *in vitro* activity listing to the *in vitro* and clinical infections listing and the addition of "Group A" after *Streptococcus pyogenes* and "Group B" after *Streptococcus agalactiae*. The agency no longer uses the designation of "Group A" after a listing of *S. pyogenes* since this species is well recognized as belonging to this group. The designation of "Group B" after a listing of *S. agalactiae* has also recently been eliminated.

The movement of *Staphylococcus saprophyticus* into the clinical efficacy listing will depend on the approval of this organism for the indication of uncomplicated urinary tract infections. Since no data were included with this submission and this submission is cross-referenced to NDA 20-634—levofloxacin tablets, the listing of *Staphylococcus saprophyticus* will depend on the data contained in and approval of the relevant supplement to NDA 20-634.

CONCLUSIONS & RECOMMENDATIONS:

This NDA supplemental application requests approval for uncomplicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*. The approval of this indication will depend on the data included in NDA 20-634 (levofloxacin tablets) and its approval since no data are included in this submission.

If the above indication for *Staphylococcus saprophyticus* is approved then this organism may be moved from the *in vitro* activity only listing to the listing with clinical efficacy in the microbiology section of the label.

The addition of "Group A" after *Streptococcus pyogenes* and "Group B" after *Streptococcus agalactiae* should not be allowed. The agency no longer uses the designation of "Group A" after a listing of *S. pyogenes* since this species is well recognized as belonging to this group. The designation of "Group B" after a listing of *S. agalactiae* has also recently been eliminated.

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ON ORIGINAL

The sponsor should be notified of the following:

1. If levofloxacin is approved for uncomplicated UTI caused by *Staphylococcus saprophyticus* then this organism may be placed in the microbiology section of the label in the listing that has both *in vitro* activity and clinical efficacy. If this occurs then the organism should be removed from the *in vitro* activity only listing.

2. The designation "Group A" after *Streptococcus pyogenes* should be deleted. The agency no longer uses the designation of "Group A" after a listing of *S. pyogenes* since this species is well recognized as belonging to this group.

3. The designation "Group B" after *Streptococcus agalactiae* should be deleted. The designation of "Group B" after a listing of *S. agalactiae* has also recently been eliminated by the Agency since this species is well recognized as belonging to this group.

/S/

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir /S/ Signature 9/10/98 Date
HFD-590/TLMicro /S/ Signature 7/23/98 Date

CC:
HFD-590/Original NDA # 20635/SLI-003
HFD-590/Division File
HFD-590/TLMicro/SLard
HFD-590/Micro/PDionne
HFD-590/MO/RHopkins
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/RAnderson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NOV 3 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-634/S-004 **SUBMISSION DATE:** June 4, 1998
Levofloxacin, 250 & 500 mg tablets

R.W. Johnson **REVIEWER:** Funmilayo O. Ajayi, Ph.D.
Pharmaceutical Research Institute,
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869 **TYPE OF SUBMISSION:** Supplement (SE1)

BACKGROUND: The sponsor provides information in support of an application for a new indication, uncomplicated urinary tract infection. The supporting data contained in the pharmacokinetics section of the current application was submitted as part of the original NDA. This data has been previously reviewed and found acceptable. In addition, the sponsor is not requesting new changes to the Clinical Pharmacology section of the product label.

APPEARS THIS WAY
ON ORIGINAL

FINDINGS: The mean urinary concentration over a period of 36 hours following administration of a 250 mg oral dose is contained in Table 1. The urinary concentrations for the 24 - 36 h collection interval for most subjects (except 1 at 1 occasion; **see the Attachment**) were well above the literature MIC_{90} values of the pathogens commonly found in uncomplicated urinary tract infection (Table 2). There are no formulation changes. The approved 250 mg tablets will be marketed for this indication if approved.

APPEARS THIS WAY
ON ORIGINAL

Table 1: Mean ± SD concentrations of Levofloxacin in the urine of healthy volunteers after a 250 mg oral dose (study LOFBO-PHI0-096)

Collection Interval	Concentration in Urine (μg/ml)	
	Treatment A*	Treatment B**
0 - 12 h	110 ± 32	108 ± 31
12 - 24 h	77 ± 30	63 ± 22
24 - 36 h	19 ± 8	17 ± 7
No of subjects	15	16

* Levofloxacin adminstered as 2 x 125 mg tablets; 1 subject withdrew after completing treatment B

** Levofloxacin adminstered as one 250 mg tablet

Table 2: MIC_{90} values of the pathogens commonly found in uncomplicated urinary tract infection (as reported by the sponsor)

Organism	MIC_{90} (μg/ml)
Escherchia Coli	0.10
Proteus mirabilis	0.125
Klebsiella pneumoniae	0.25
Staphylococcus saprophyticus	0.5
Streptococcus agalactiae (Group B)	1.0
Enterococcus faecalis	2.0

RECOMMENDATION: The submitted information has been reviewed and found acceptable.

/S/ 11/3/98

Funmilayo O. Ajayi, Ph.D.
Div. of Pharmaceutical Evaluation III

/S/

FT initialed by Frank Pelsor, PharmD.....11/3/98

cc: NDA 20-634 HFD-590 (Clinical Division)
HFD-590 (Hopkins)
HFD-880 (DPE3,Pelsor,Ajayi)
CDR (B. Murphy)

Attachment

APPEARS THIS WAY
ON ORIGINAL

Table SD1: Concentrations of Levofloxacin in the Urine of Healthy Volunteers after a 250-mg Oral Dose of Levofloxacin
(Data obtained from Study LOFBO-PHI0-096)

Subject No.	Concentration in the Urine Treatment A[a] (µg/mL) 0-12 (h)	12-24 (h)	24-36 (h)	Concentration in the Urine Treatment B[a] (µg/mL) 0-12 (h)	12-24 (h)	24-36 (h)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13[b]						
14						
15						
16						
Mean	109.99	77.02	18.98	107.92	63.27	16.87
SD	32.28	29.77	7.70	30.53	21.92	6.68
CV %	29	39	41	28	35	40

[a] Administered as two 125-mg clinical tablets in Treatment A and one 250-mg marketed-image tablet in Treatment B.

[b] Subject withdrew from the study after completion of one study period (market-image tablet) due to an upper respiratory tract infection.

APPEARS THIS WAY
ON ORIGINAL