CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

MEDICAL REVIEW(S)

DEC 15 1998

NDA 20-634 Levofloxacin for uncomplicated UTI

Title: Medical officer's review of supplemental NDA
NDA number 20-634

Applicant identification

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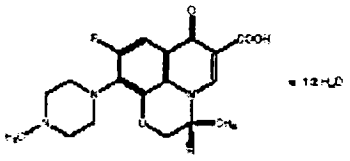
Submission/review dates
Date of submission: June 4, 1988
Date submission received by reviewer: August 3, 1998
Date review begun: August 6, 1998
Date review completed: November 19, 1998

Drug identification:

Generic name: levofloxacin tablets
Trade name: Levaquin tablets
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
Molecular weight: 370.38
Pharmacologic category: Flourinated carboxyquinolone
Dosage form: tablet
Route of administration: oral

Proposed additions to the label (highlighted):

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
Staphylococcus aureus
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes (Group A)

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

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INDICATIONS AND USAGE

LEVAQUIN Tablets 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:

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*.

Community-acquired pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES.**)

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

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 *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* 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.

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DOSAGE AND ADMINISTRATION

The usual dose of LEVAQUIN Tablets is 500 mg orally every 24 hours as described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., CL_{CR} >80 mL/min). For patients with altered renal function (i.e., CL_{CR} ≤80 mL/min), 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, or aluminum, as well as sucralfate, metal cations such as iron, and multi-vitamin preparations with zinc.

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
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Acute Maxillary Sinusitis	500 mg	q24h	10-14 days	500 mg
Uncomplicated SSSI	500 mg	q24h	7-10 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**.)

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		
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 UTI / Acute Pyelonephritis		
CL_{CR} ≥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.

Material reviewed: Material supporting this NDA included the report of a single study LOFBO-UTI-060; (a controlled study comparing a three day course of levofloxacin with a three day course of ofloxacin for the treatment of uncomplicated UTI), in vitro microbiological data, and a cumulative drug safety database incorporating other studies and post marketing data.
Safety data was derived from the pooled experience in 15 phase three studies reported in the original levofloxacin submission and 3 subsequent clinical trials.

Introduction : A variety of agents are indicated for the treatment of uncomplicated urinary tract infections in women. Treatment regimens range from 14 days to as little as a single dose with a general trend to decreasing treatment times as newer agents are identified. Selection of a suitable agent is influenced by among other factors, the identification and sensitivity of the infecting organisms. Existing agents are approved for use against a battery of pathogens on the basis of clinical efficacy and in vitro activity. For given indications, such as in this case uncomplicated UTI's in women, treatment regimens are described for a limited and specific group of pathogens. Older agents including nitrofurantoin, naladixic acid, trimethoprim and trimethoprim /sulphamethoxazole are used for periods of 7 to 14 days for the treatment of uncomplicated UTI in women. Highly active fluoroquinolones have allowed the duration of treatment to be reduced to three days with acceptable eradication rates for specified pathogens. Other organisms may require longer treatment regimens in this setting. Table 1 summarizes the non-fluoroquinolone agents approved by the FDA for uncomplicated UTI.

Table 1: FDA approved non-fluoroquinolone agents for uncomplicated UTI

Drug	Organisms	Duration of therapy
Nitrofurantoin	*E coli, Staph saprophyticus, enterococcus,staph aureus, klebsiella pneumoniae enterobacter sp*	7 days
Naladixic acid	*E coli, enterobacter, Klebsiella sp, proteus sp*	7-14 days
Trimethoprim	*E coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter, Staph saprophyticus*	10 days
Fosfomycin /tromethamine	*E coli, enterococcus faecalis*	Single dose
Timethoprim/ Sulphamethoxazole	*E coli, Klebsiella sp,Enterobacter sp, Morganella morganii, Proteus mirabilis* and *vulgaris*	10-14 days

Several fluoroquinolones are currently indicated for uncomplicated UTI's based on supportive clinical data, good urinary penetration and a broad spectrum of susceptible organisms. They may demonstrate superior efficacy with shorter durations of treatment. Pathogen eradication rates (5 to 11 days post therapy) have been reported at 76% for 7 days of nitrofurantoin, 83% for a single dose of fosfomycin tromethamine, 98% for 10 days of trimethoprim sulphamethoxazole and 98% for 7 days of ciprofloxacin. Three day regimens are approved for selected fluoroquinolones as shown below.

Table 2: FDA approved fluoroquinolone agents for uncomplicated UTI

Drug	Organisms	Duration of therapy
Ciprofloxacin	*E coli, staph saprophyticus*	3 days
Norfloxacin	*E faecalis, e coli, klebs pneumoniae, proteus mirabilis, pseudomonas aeruginosa, staph epi, staph saprophyticus, citrobacter freundii *enterobacter aerogenes, e cloacae*, proteus vulg*, staph aureus*, strep agalactiae**	3 days
Trovofloxacin	*E coli*	3 days
Ofloxacin	*E coli, klebs pneumoniae, citrobacter diversus,enterobacter aerogenes,proteus mirabilis pseudomonas aeruginosa*	3 days
Enoxacin	*E coli, staph epiderm*, staph saprophyticus**	7 days
Lomefloxacin	*E coli, Klebs pneumoniae, proteus mirabilis, staph saprophyticus*	10 days

* clinical efficacy reported for less than 10 cases

Levofloxacin, first approved in tablet form on 12/20/96, is currently indicated for the treatment of acute maxillary sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia, uncomplicated skin and skin structure infections, complicated urinary tract infections and acute pyelonephritis due to certain organisms. It is excreted in the urine in high concentration. This is supported by data from the sponsor showing a range of concentrations between 17 and 110 µg/ml in the urine of 16 volunteers over a collection period of 36 hours. (MIC90 values range from 0.1 to 2.0 µg/ml for pathogens commonly associated with uncomplicated UTI.) Levofloxacin is active against a broad spectrum of gram positive and negative organisms. However, in this application, the sponsor has included reports of resistance in two sets of isolates of *Enterococcus faecalis* and other organisms with specific resistance mechanisms. The current application seeks to extend the indications for levofloxacin to include 3 day treatment of uncomplicated UTI with the following organisms: *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Staph saprophyticus*. The dosage to be used is 250mg q24 for 3 days.

The indication "Uncomplicated Urinary tract Infection" is defined according to the FDA CDER anti-infective drugs guidance document, as a clinical syndrome in women characterized by dysuria, frequency, and/or urgency in combination with pyuria and bacteriuria where there is no known underlying renal or urologic dysfunction or obstruction. Sources differ on the cutoff diagnostic colony count for urinary pathogens. The Anti-infective Advisory Committee (July 1998) recommended a count $>=10^5$cfu/ml for study inclusion as significant pathogens and a count $<=10^4$ cfu/ml to define eradication. Others have recommended using a colony count $=>10^3$ cfu/ml for inclusion of a single species of uropathogen in studies (CID 1992;15 Suppl1:s216-227). Gram positive organisms causing UTI *eg Staph saprophyticus* tend to appear in lower concentrations than gram-negative organisms.

This application is supported by a) in vitro microbiological data, b) a clinical equivalence trial comparing levofloxacin and ofloxacin given as a three-day regimen for uncomplicated UTI's, and c) a cumulative drug safety database incorporating other studies and post marketing data. The focus of this review will be the clinical equivalence trial and supportive safety data.

Indication: uncomplicated UTI

Trial #1 Uncomplicated UTI: Study LOFBO-UTI-060

Objective: To demonstrate equivalence of levofloxacin and ofloxacin in the treatment of uncomplicated UTI.

To support the proposed new indication of uncomplicated UTI for levofloxacin, the safety and efficacy of a three day course of levofloxacin 250mg given once daily was compared with a three day course of ofloxacin, 200mg given twice daily to patients with uncomplicated UTI.

Treatments: Levofloxacin 250mg q 24 hours X 3 days
Ofloxacin 200mg q 12 hours X 3 days

Design: This was a randomized, double blinded study comparing a three day regimen of levofloxacin at a dose of 250mg daily PO with FLOXIN 200mg PO b.i.d. for three days in the treatment of uncomplicated urinary tract infections.

The schedule of study procedures are shown in Table 1:

Table 1: Schedule of Study Procedures
(Protocol LOFBO-UTI-060)

Assessment/Procedure	Admission[a]	Last Day of Therapy	Interim[b] Evaluation (Phone Contact)	Posttherapy[c] (test-of-cure)	Poststudy (Long-Term)[d]
Pertinent Medical History	X				
Pregnancy Test[e]	X			X	
Study Drug Administration	X----------X				
Efficacy Evaluations					
Clinical					
- Clinical Signs/Symptoms	X		X	X	X
Clinical Response Rating				X	X
Microbiologic					
- Urine Culture	X		X[f]	X	X
- Susceptibility Test	X		X[f]	X	X
Safety Assessments					
Adverse Events	X[g]	----------X			
Clinical Laboratory Tests					
- Hematology	X			X	
- Serum Chemistry	X			X	
- Urinalysis	X		X[f]	X	X
Pertinent Physical Exam (including Vital Signs)	X			X	

[a] Must be obtained 548 hours prior to treatment.
[b] Study Day 3-5 (Phone contact).
[c] 5-9 days after completion of study drug.
[d] 4-6 weeks after completion of study drug, subjects with an admission pathogen and clinical success (cure or improved) at the posttherapy visit only.
[e] For women of childbearing potential.
[f] If not making significant clinical improvement.
[g] Following first dose of study drug.

Cross-reference: Appendix 1.1.

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Suitable patients were seen according to the following schedule:

On admission, a history of symptoms was recorded. A physical examination was performed and baseline laboratory investigations including hematology, serum chemistry and a pregnancy test were done. A pre-therapy urine was obtained and tested for culture, sensitivity and urinalysis. Patients were then randomized to receive either levofloxacin or ofloxacin. (Admission information and investigations had to be obtained within <=48 hours before starting medication).

Between days three and five, subjects were contacted by phone and questioned about ongoing symptoms of UTI and of possible adverse effects from the treatment. At the physicians' discretion a visit could be scheduled to evaluate complaints. If symptoms of UTI persisted, a repeat urine culture was obtained. If an organism was cultured and shown to be resistant to both agents, but the subject was improving clinically, she could continue with the study drug. At this visit, subjects showing no improvement were classified as treatment failures provided they had received at least 48 hours of the study drug.

The post therapy visit was scheduled between days 5 and 9 after completion of therapy. This visit was used to determine microbiological efficacy. A clean catch midstream or straight catheterization urine was obtained for urinalysis, culture and sensitivity. Hematology and blood chemistries were repeated and a record of symptoms, concomitant medications and relevant physical signs was obtained.

A post study visit (4 to 6 weeks after completion of therapy) was scheduled for only those patients who had positive admission cultures (>= 10^3cfu/ml) and who were considered to be clinical successes at the post therapy visit. The purpose of this visit was to determine persistence or relapse of the original infection or the presence of a new infection. At this visit a urinalysis, urine culture and sensitivity were obtained and a record of clinical symptoms and signs was made.

Inclusion criteria:
All study subjects were non-pregnant young women giving no history of recent urinary tract instrumentation , recent antimicrobial use or known functional or anatomical urinary tract abnormalities. The definition of an uncomplicated UTI relied on the presence in the urine of >=10^5 cfu/ml of a uropathogen in the presence of pyuria, and either urinary urgency, frequency or dysuria (pain and/or burning). A subset of patients with colony counts >= 10^3 and <10^5 cfu/ml was also examined.

Exclusion criteria:
Subjects with a history of UTI symptoms for longer than 7 days, functional or anatomic abnormalities of the urinary tract, antibiotic use within the past 48 hours, or pyelonephritis or those requiring a non-study systemic antimicrobial were excluded. Subjects with seizure disorders or unstable psychiatric conditions and elderly or pregnant women were also excluded.

Randomization and blinding:
Computerized randomization generated equal numbers of patients in each arm. All study personnel, monitors and statisticians remained blinded to the study drug.

Dosage and administration:
Subjects assigned to receive levofloxacin received one 250mg tablet of levofloxacin once daily and one matching placebo once daily for three days. Subjects randomized to receive ofloxacin received one 200mg tablet twice daily for three days.

Compliance
Compliance was determined by counting unused study drug in the returned blistercards.

Concomitant medications
The use of non-study systemic antimicrobials and oral urinary tract antiseptic agents was prohibited during the study. The use of aluminum/magnesium based antacids and minerals was discouraged because of the likely effects on quinolone absorption. Where unavoidable they were to be used at least two hours before or after study drug administration.

Efficacy and safety evaluations:

The sponsor identified the following populations for evaluation:
Intent-to-treat (all enrolled subjects regardless of initial urine culture result)
Modified intent-to–treat (all enrolled subjects with a positive admission urine culture =>10^5 cfu/ml)
Fully microbiologically evaluable (see below under "primary population for review")
Fully microbiologically evaluable from centers with more than 10 suitable subjects
Possibly microbiologically evaluable (those with urine pathogen counts >= 10^3 but<10^5 cfu/ml and clinical signs and symptoms of an acute uncomplicated UTI).

The primary efficacy variable was the microbiological response rate. Response rates to individual pathogens were separately analyzed.

The sponsor also reported efficacy based on pre- and post-therapy clinical signs and symptoms.

Safety was evaluable if the subject had taken at least one dose of the study drug and some postadmission safety information was available.

Primary population for review:
The primary population reviewed by the sponsor was the group designated "fully microbiologically evaluable". This included all patients with admission urine cultures positive for urinary pathogens at a concentration >=10^5cfu/ml for whom a post therapy culture was available

In addition, microbiological efficacy was not determined in patients who:

a) Were not evaluable for safety (did not take at least one dose of study drug or had no post-admission safety data)
b) Had an absence of bacteriologically proven infection (i.e. no definite admission pathogen isolated in concentrations >= 10^5 cfu/ml)
c) received an insufficient course of therapy (clinical failures after taking at least 48 hours or four doses of the study drug were considered evaluable).
d) took other effective systemic antibiotics during the study period but were not judged clinical treatment failures
e) had missing or inappropriate urine cultures:
   Admission cultures taken after the first dose of antibiotic or >48 hrs prior to admission to the study,
   Post-therapy cultures taken earlier than 5 days after completing therapy or later than 12 days after completing therapy
   missing post-therapy cultures
   Clinical failures with no valid post-therapy culture were regarded as evaluable (presumed persistence)
f) were lost to follow up (despite providing safety information) or were guilty of other protocol violations.

The reviewer concurred that this was the primary population of interest. However polymicrobial cultures were difficult to interpret. The reviewer identified the primary population for review as those patients who were fully microbiologically evaluable, and who presented with infection due to a single uro-pathogen in concentrations >=10^5cfu/ml.

Additional populations examined in this review included
1) those patients with initial urine cultures positive for a single urinary pathogen at concentrations >=10^3 cfu/ml but <10^5 cfu/ml (designated "possibly microbiologically evaluable" by the sponsor).
2) groups of patients from the "fully microbiologically evaluable population" described above with initial cultures positive for selected pathogens.

Microbiological responses were classified by the sponsor as:

Eradicated: <10^3 cfu/ml of the uropathogen present on admission in the post therapy culture in the absence of potentially effective antibiotics.

Persisted: >=10^3 cfu/ml of the uropathogen present on admission in the post therapy culture.

Presumed persisted: Presumed persistence in subjects with "clinical failure" at the post-therapy visit where

a) no post-therapy culture was taken,
b) the patient was on potentially effective antibiotics
c) a negative culture less than five days after the last dose of the study drug

Persistence with acquisition of resistance: >=10^3 cfu/ml of the original pathogen in the post-therapy urine showing resistance.

Unknown:

a) no post-therapy urine

b) patients who improved or were cured clinically with negative post-therapy cultures, who were however receiving potentially effective antibiotics.

Patients with a successful clinical outcome (cured or improved) at the post therapy visit were evaluated microbiologically four to six weeks after completion of the course of antibiotics (the post-study visit). At this point, outcomes were classified as:
Eradicated: $<10^3$ cfu/ml of the initial pathogen (including subjects with a positive culture in the post-therapy urine).
Persisted: $>= 10^3$ cfu/ml of the original pathogen (included subjects evaluated as "clinically cured" at the post-therapy visit).
Microbiological relapse: Reappearance of the admission pathogen at the same or greater colony count as in the pre-study urine, following previous eradication at the post-therapy visit.
Presumed microbiological relapse: Patients treated with antibiotics for a relapse of symptoms at the post-study visit with no microbiology result before starting the antibiotic.
Unknown: No culture, or a negative culture when antibiotics were administered between the post-therapy and post-study visits.

Subsequent to the development of the protocol, subjects with pathogens $>=10^3$ cfu/ml and $<10^5$ cfu/ml at the post-study visit were regarded as a) "relapse" if symptomatic, b) "relapse" if asymptomatic but received effective concomitant therapy or c) "eradication" if asymptomatic with no concomitant medication.
Clinical response
A comparison of signs and symptoms on admission with those at the post-therapy visit was interpreted by the sponsor as follows:
Cure: resolution of signs and symptoms
Improved: partial resolution of signs and symptoms compared to baseline with no need for further treatment. This included subjects who discontinued the study early but previous assessment demonstrated improvement.
Failure: non-resolution requiring further antibiotics
Unable to evaluate: patients lost to follow up

Compared to the post-therapy visit, the outcome at the post-study visit was interpreted as:
Cure
Clinical relapse or new infection: recurrence of signs or symptoms of UTI requiring antibiotic therapy.
Unable to evaluate: loss-to-follow-up or those receiving an effective antibiotic for another indication after completion of the initial antibiotic regimen.

Safety evaluation: included adverse events reported by patients to non-leading questions at each study visit and telephonic reports between visits, pertinent physical and vital sign abnormalities detected at study visits and abnormalities of hematology, serum chemistry and urinalysis.
Statistical methods:
The primary efficacy variable was microbiological eradication (evaluated by pathogen).
The secondary efficacy variable was the clinical response.

Equivalence with comparator arm was evaluated by the sponsor using 95% confidence intervals around the difference between the arms. Cure rates were determined for patients with complete microbiological data. Subgroup analyses were performed on intent-to-treat groups, modified intent-to-treat groups and subjects from high enrolling centers. Results were further analyzed according to individual pathogens.

MO comments on endpoints:

A baseline colony count of $=>10^5$ cfu/ml is recommended for the diagnosis of a urinary tract infection with a given organism (CID 1992;15: S216-S227) resulting in a high degree of diagnostic specificity. Borderline counts between 10^3cfu/ml and 10^5 cfu/ml may not indicate true UTI and such findings would also be compatible with contamination due to poor collection technique or prolonged processing times. In these instances a repeat culture showing the same pathogen would be helpful. The protocol under review did not

accommodate this since antibiotic treatment was initiated on clinical grounds before culture results were available. According to FDA guidelines, an endpoint of =<10^4 cfu/ml is regarded as an acceptable cutoff for cure. The more stringent endpoint in this study =<10^3cfu/ml would be acceptable for pathogens present in concentrations >=10^5 cfu/ml on admission.

Urine specimens with multiple organisms are less reliable in indicating a true UTI. For example perineal contamination with *Enterococci* or *Staphylococcus epidermidis* may misleadingly suggest a polymicrobial UTI. On this basis a reviewer analysis has been performed on the subset of infections with admission colony counts =>10^5 cfu/ml where evaluability is not confounded by polymicrobial cultures.

Infections with Staphylococcus saprophyticus may occur at low colony counts. The reviewer has accepted a colony count >=10^3cfu/ml as indicative of infection with this organism.

In this study, eradication of pathogens depended on at least a 2 log decrease in the colony count of patients with an admission count =>10^5 cfu/ml. However cases with admission counts >=10^3cfu/ml and <10^5 cfu/ml were also required to fall <10^3cfu/ml to be evaluated as cures. In these cases discrimination between cure and persistence may be unreliable. Further, at the post study visit, colony counts only had to fall to >=10^3cfu/ml and <10^5 cfu/ml to be classified as eradication (provided patients were asymptomatic and not on antimicrobials). In such cases persistence or relapse cannot be excluded.

Results:

Table 3. Populations for analysis:

	Levofloxacin	Ofloxacin
Total enrolled (ITT)	298	296
Fully micro evaluable	157	165
Admission cfu<=10^5/ml	131	118
Possibly micro eval <10^5/ml>=10^3/ml	55	49
Admission cfu<10^3/ml	76	51
Unsuitable follow up data	10	13

On an intent-to-treat basis 594 subjects with symptoms of uncomplicated UTI were enrolled at 23 study centers in the USA; 298 received levofloxacin and 296 ofloxacin.

Premature withdrawals occurred in 3 levofloxacin recipients and 5 ofloxacin recipients for the reasons shown in the table below.

Table 4: Reasons for premature withdrawal

	Levofloxacin (N=298)		FLOXIN (N=296)	
Reason for Premature Withdrawal	No.	(%)[a]	No.	(%)[a]
Adverse Event	0	(0.0)	4	(1.4)
Clinical Failure	1	(0.3)	0	(0.0)
Personal Reason	0	(0.0)	1	(0.3)
Other[b]	2	(0.7)	0	(0.0)
Total Who Withdrew	3	(1.0)	5	(1.7)
Total with Completion/Withdrawal Information	296		293	
Total with Unknown Completion/ Withdrawal Information	2		3	

[a] Percentages based on total number with completion/withdrawal information.
[b] Subject 15023: misdiagnosed as UTI; subject 18015: protocol violation (complicated UTI).

MO comment: Of the initial 594 symptomatic subjects, 131 (44%) levofloxacin recipients and 118 (40%) ofloxacin recipients did not have a diagnostic initial urine culture (>=10^5cfu/ml). This suggested that symptoms would be an unreliable indicator of the microbiological responses to treatment.

Of the 343 patients with diagnostic urine cultures on entry, 10 levofloxacin and 13 ofloxacin recipients were not suitable for microbiological evaluation as detailed below.

Table 5 Sponsor's reasons for failing to meet microbiological evaluability criteria:

	Levofloxacin	**Ofloxacin**
Bacteriologic infection not proven	131	118
Effective concom Rx	4	0
Inappropriate bacteriol culture	4	7
Insufficient antibiotic	1	3
Unevaluable for safety	0	3
Other protocol violations	1	0
Total	141 (47.3%)	131 (44.3%)

Demographic characteristics are presented in the table below. No significant differences were noted between the arms.

Table 1: Demographic and Baseline Characteristics: Intent-to-Treat Population (Protocol LOFBO-UTI-060)

	Levofloxacin (N=298)	FLOXIN (N=296)	Overall Total (N=594)
Sex			
Women	298 (100.0)	296 (100.0)	594 (100.0)
Race			
Caucasian	231 (77.5)	230 (77.7)	461 (77.6)
Black	49 (16.4)	49 (16.6)	98 (16.5)
Oriental	6 (2.0)	11 (3.7)	17 (2.9)
Hispanic	9 (3.0)	4 (1.4)	13 (2.2)
Other	3 (1.0)	2 (0.7)	5 (0.8)
Age (Years)			
≤45	255 (85.6)	258 (87.2)	513 (86.4)
46-64	43 (14.4)	37 (12.5)	80 (13.5)
≥65	0 (0.0)	1 (0.3)	1 (0.2)
N	298 (100.0)	296 (100.0)	594 (100.0)
Mean±SD	31.3±11.08	32.0±10.58	31.6±10.83
Range			
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Weight (lbs)			
N	296 (99.3)	294 (99.3)	590 (99.3)
Mean±SD	149.6±39.26	149.4±38.14	149.5±38.67
Range			
Missing	2 (0.7)	2 (0.7)	4 (0.7)
Height (inches)			
N	294 (98.7)	291 (98.3)	585 (98.5)
Mean±SD	64.7±2.76	64.5±2.58	64.6±2.67
Range			
Missing	4 (1.3)	5 (1.7)	9 (1.5)

NOTE: Values represent number (%) of subjects except as otherwise indicated.

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Most patients (77.6%)were Caucasian.

Compliance with dosing was high. In a small number of patients the 6 study doses overlapped a 4th day as shown below

Table 6 Compliance with dosage schedule

	Levofloxacin	Ofloxacin
3 days	95.6%	94.9%
4 days (still 6 doses)	4.4%	2.7%

Concomitant therapy:
Concomitant antimicrobials were received by patients in both arms of the study. Those patients given effective antimicrobials prior to randomization or prior to the post-therapy visit were unevaluable

Table 7 Numbers of patients in each arm who received concomitant antimicrobials:

	Levo floxacin	Ofloxacin
Total	20 (6.7)	14 (4.7)
Antibiotic prior to randomization (culture neg)	4	3
Antibiotic prior to post therapy visit	3	0

MO Comment: Concomitant antibiotics were used by 7 patients prior to randomization, rendering their initial cultures negative. Three levofloxacin recipients received antibiotics prior to the post-therapy visit rendering them microbiologically unevaluable. The antibiotics were given for symptoms unrelated to UTI and included penicillin in one, keflex in one, and ceftin, rocephin and biaxin in one. The initial urinary tract pathogens in these patients were *E coli* in two and *M morgani* and *S aureus* in one. The reviewer agreed that these should be regarded as unevaluable rather than treatment failures.
The other 24 patients reportedly either received their antibiotics after the post therapy visit, received anti-fungals rather than antimicrobials, received antibiotics not active against the infecting organism or were switched following therapeutic failure. Concomitant antibiotic use appeared equivalent for both groups

Concomitant use of other agents was similar for both groups as shown below.

Table 8 Concomitant medications received by patients in each study arm

	Levofloxacin (N=298)		FLOXIN (N=296)	
Therapy Classification	No.	(%)[a]	No.	(%)[a]
Total Who Took Concomitant Therapy	224	(75.2)	211	(71.3)
Central Nervous System	65	(21.8)	66	(22.3)
Antimicrobials	20	(6.7)	14	(4.7)
Vitamins & Nutritional Supplements	13	(4.4)	11	(3.7)
Antacids	9	(3.0)	7	(2.4)
NSAID	3	(1.0)	2	(0.7)
Corticosteroids	1	(0.3)	0	(0.0)
Anticoagulants	0	(0.0)	1	(0.3)
Total with Concomitant Therapy Info.	298		296	

[a] Percentages based on total number of subjects with concomitant therapy information available.

Table 9 Numbers of patients randomized and number of patients microbiologically evaluable at each study center.

	Levofloxacin			FLOXIN		
Investigator[a]	Intent-To-Treat	Micro Evaluable		Intent-To-Treat	Micro Evaluable	
Bowen, Bruce, M.D.	14	10	(71.4)	15	9	(60.0)
Brecher, David, M.D.	1	0	(0.0)	0	0	(0.0)
Cox, II, Clair, M.D.	2	2	(100.0)	1	1	(100.0)
DeAbate, C. Andrew, M.D.	35	22	(62.9)	33	16	(48.5)
DeHart, Del, M.D.	7	3	(42.9)	6	1	(16.7)
Duckett, Melvin, M.D.	1	0	(0.0)	0	0	(0.0)
Edmunds, Keith, M.D.	13	7	(53.8)	15	6	(40.0)
Forbes, Ray, M.D.	16	9	(56.3)	18	10	(55.6)
Gecys, Gintare, D.O.	1	1	(100.0)	3	0	(0.0)
Gilkey, John, M.D.	3	1	(33.3)	4	2	(50.0)
Hedrick, Richard, M.D.	6	3	(50.0)	3	3	(100.0)
Hirsh, Robert, M.D.	15	6	(40.0)	16	8	(50.0)
King, William, M.D.	1	1	(100.0)	0	0	(0.0)
Klein, Steven, M.D.	22	9	(40.9)	23	13	(56.5)
Kupersmith, Stephen, M.D.	11	5	(45.5)	10	7	(70.0)
Larach, Fernando, M.D.	2	1	(50.0)	0	0	(0.0)
Mumper, James, M.D.	15	5	(33.3)	14	7	(50.0)
Puopolo, Anthony, M.D.	13	5	(38.5)	12	6	(50.0)
Richard, George M.D.	44	22	(50.0)	45	26	(57.8)
Ruoff, Gary, M.D.	29	19	(65.5)	28	16	(57.1)
Solomon, Eric, M.D.	27	14	(51.9)	27	14	(51.9)
Tepper, Daniel, M.D.[b]	14	10	(71.4)	17	15	(88.2)
Tice, Alan, M.D.	6	2	(33.3)	6	5	(83.3)
Total	298	157	(52.7)	296	165	(55.7)

[a] Dr. Kalet did not enroll any subjects and is therefore not included in this list.

[b] Tepper, Daniel was replaced at this site by Buchanan, Christopher J.

Note: Numbers shown in parentheses are percentages for that category.

Percentages enrolled patients found to be fully microbiologically evaluable averaged 52.7% in the levofloxacin group and 55.7% in the ofloxacin group.

Table 10 Antibiotic susceptibility of isolates on admission for each treatment arm:

	Levofloxacin	Ofloxacin
Number of admission isolates	204	200
Number with susceptibility data	203	196
Number of resistant isolates	1	0

The single resistant isolate was a *Staph aureus* which was found to be resistant to both levofloxacin and ofloxacin.

Microbiological eradication rates as determined by sponsor

For levofloxacin and ofloxacin respectively, eradication rates of 96.2%and 94.5% were reported by the sponsor in patients who were fully microbiologically evaluable with admission cultures >=10^5 cfu/ml. 86.4% and 94.2% of pathogens in each respective arm were gram negative aerobes and 13.6% and 5.8% respectively were gram positive aerobes. Gram negative eradication rates were equivalent between the arms (97.9% vs 96.3% respectively). Levofloxacin resulted in higher gram positive eradication rates than ofloxacin (20 of 23 cases vs 7of 10 cases respectively). The major difference was in eradication of *E faecalis* (5 of 5 cases vs 1 of 2 cases respectively).

The following table summarizes microbiological eradication rates in patients with admission cultures >=10^5cfu/ml, shown for individual pathogens.

Table 12b: Microbiologic Eradication Rates Based on Definite (≥10^5 cfu/mL) Admission Pathogens Summarized by Pathogen Category and Pathogen: Subjects Fully Evaluable for Microbiologic Efficacy (Protocol LOFBO-UTI-060)

Urine Cultures:	Levofloxacin		FLOXIN		
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]	95% CI[b]
Pathogen Category					
gram positive aerobic pathogens	23	20 (87.0)	10	7 (70.0)	(-53.5, 19.6)
gram negative aerobic pathogens	146	143 (97.9)	164	158 (96.3)	(-5.6, 2.4)
Total by pathogen	169	163 (96.4)	174	165 (94.8)	(-6.2, 3.0)
Total by subject[c]	157	151 (96.2)	165	156[d] (94.5)	(-6.5, 3.3)
Pathogen[e]					
Escherichia coli	121	119 (98.3)	134	128 (95.5)	(-7.4, 1.8)
Klebsiella pneumoniae	9	8 (88.9)	8	8 (100.0)	
Streptococcus (Enterococcus) faecalis	5	5(100.0)	2	1 (50.0)	
Staphylococcus saprophyticus	8	8(100.0)	1	1 (100.0)	
Proteus mirabilis	7	7(100.0)	14	14 (100.0)	
Streptococcus agalactiae[f]	5	3 (60.0)	5	3 (60.0)	

[a] Numbers shown in parentheses are percentages for that category.

[b] Two-sided 95% confidence interval around the difference (FLOXIN minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.

[c] Eradication of all definite pathogens isolated for a subject at admission.

[d] Three FLOXIN-treated subjects (4020, 8012, and 65027) who are included in this analysis as having an infection outcome of eradicated are considered as having persistence of their infection when both definite and possible admission pathogens are considered (as in Table 12a and the CANDA data base).

[e] N≥5 for either treatment group. Multiple strains are counted separately.

[f] Subject 15003 (levofloxacin) was erroneously excluded from the analyses (see Section 4.6.1). This subject should have been counted as a clinical cure with microbiologic persistence, thus the eradication rate for

MO comment:
Owing to small numbers of subjects per treatment arm for infections with *Enterococcus faecalis*, *Staphylococcus saprophyticus*, and *Strep agalactae*, claims of comparative efficacy were poorly supported. To date, neither levofloxacin nor ofloxacin are approved for the treatment of uncomplicated UTI due to *Enterococcus faecalis*. In particular, there were only 5 cases of *E faecalis* in the levofloxacin group and 2 in the ofloxacin group. Of these, 1 patient failed therapy in the ofloxacin group.

It was noted that several admission urine cultures yielded polymicrobial results. It was anticipated that uncomplicated UTI's in young women were most likely to be caused by a single organism. Polymicrobial cultures may indicate defects in sample collection techniques or delays in processing, where contaminants would reach concentrations of "clinical significance". Fifty- six admission cultures yielded more than one organism growing at various concentrations. Fourteen of these polymicrobial admission cultures yielded more than one organism in concentrations of >=10^5 cfu/ml. The results were re-evaluated in the population of fully microbiologically evaluable patients excluding these 14 as shown below.

Table 11 Numbers of patients with polymicrobial infections by study center

Center	N	Polymicrobial (all organisms >=10^3cfu/ml)	Polymicrobial (2 or more organisms >=10^5cfu/ml)
Bowen	19	0	0
Brecher	4	0	0
De Abate	68	15	4
DeHart	13	0	0
Ducket	1	0	0
Edmunds	28	4	0
Forbes	34	4	0
Gecys	4	0	0
Gilkey	7	0	0
Hedrik	9	0	0
Hirsh	31	4	1
King	2	0	0
Klein	45	5	0
Kupersmith	21	2	1
Larache	2	0	0
Mumper	29	0	0
Puopolo	25	1	1
Richard	89	9	0
Ruoff	57	6	1
Solomon	56	1	1
Tepper	30	5	5
Tice	12	0	0
TOTAL	586	56	14

MO Comment: Polymicrobial results generally constituted less than 15% of admission cultures at all centers except "De Abate" where 22% of admission cultures were polymicrobial and "Tepper" where 17% were polymicrobial. Both these centers had higher numbers of multiple pathogens at concentrations of >=10^5cfu/ml. Processing times and technical problems may have accounted for these differences.

The table below summarizes the outcome in patients with more than one admission pathogen. "Eradicated" indicates that all initial organisms isolated were eradicated "Presumed persisted" indicates that one or more of the initial infecting organisms were presumed to persist.

Table 12 Treatment group and outcome in patients with more than one admission pathogen >=10^5cfu/ml

	Levofloxacin	Ofloxacin
Eradicated	6	5
Presumed persisted	0	1
Unknown	2	0

Table 13 Reviewer defined fully microbiologically evaluable patients:

	Levofloxacin	Ofloxacin
Fully micro eval (sponsor)	157	165
Multiple organisms>=10^5cfu/ml	6	5
Fully micro eval (reviewer)	151	160

Cure rates at post-therapy visit for fully micro eval (reviewer) were 145/151 (96%) for the levofloxacin arm and 151/160 (94.4%) for the ofloxacin arm.

Table 14 Microbiological failures in patients with single admission pathogens at concentrations >=10^5cfu/ml.

	Levofloxacin	Ofloxacin
Staph saccharolyticus	1	....
E coli	2	6
Klebsiella pneumoniae	1	....
Strep faecalis	....	1
Strep agalactae	2	2

All the above organisms were persistently present at the post-therapy visit. All of these organisms were fully sensitive to both levofloxacin and ofloxacin.

Table 15 Analysis of infections at low colony counts <10^5 and >= 10^3 cfu/ml.

	Levofloxacin	Ofloxacin
Number of patients	55	49
Cures	48 (87.3%)	46 (93.9%)
Persisters	7 (12.7%)	3 (6.1%)

MOR comment: Overall pathogen eradication rates were well above the 75% rate regarded as acceptable for post treatment cultures in short course therapy (CID 1992;15 (suppl1) pS223). The reasons for treatment failure in 6 levofloxacin recipients and 9 ofloxacin recipients are unclear since all isolates were proven drug sensitive in vitro according to the protocol design. Among ofloxacin recipients, *E coli* was the etiological agent most commonly identified when therapy failed.

Relapses of original pathogens at the 4-6 week post study visit occurred according to the sponsor in 8 levofloxacin and 3 ofloxacin recipients. New infections at 4-6 weeks were seen in 3 and 2 patients respectively. Three and 11 patients respectively had presumed microbiological relapses without culture confirmation.

Relapse rates were recalculated by the FDA, using a cutoff of <10^3 cfu/ml to indicate absence of the original pathogen. Two subjects (# 6019028 and # 6007017) with post-study cultures showing the original

pathogen at concentrations >10^5 cfu/ml were erroneously designated "colonization" by the sponsor and not included as relapses. The respective pathogens in these two patients were *E coli* and *K pneumoniae*. FDA calculated relapse rates for documented relapses were 12.7% for levofloxacin and 6.7% for ofloxacin. Overall relapse rates (including documented and presumed relapses) were 14.6% for levofloxacin and 13.3% for oflaxacin.

The analysis of microbiological responses for individual pathogens was repeated, examining in detail both the number of pathogens isolated from each specimen and the number of colonies of the principle pathogen in the admission urine. Specimens where interpretation of the cultures suggested contamination or processing problems were designated unevaluable. The respective tabulations for infections *with Enterococcus, Staphylococcus saprophyticus, Streptococcus agalactae, Proteus mirabilis* and *Klebsiella pneumonia* are shown below.

Table 16 Summary of patients with *Enterococcus faecalis*

Patient #	Other organisms	Drug	Micro outcome	Reviewer evaluability
Enterococcus faecalis>=10^5cfu/ml				
06001011	-	Ofloxacin	Persisted	Yes
06004003	*Proteus mirabilis* (>=10^5cfu/ml)	Ofloxacin	Eradicated	No
06004005	*E coli* (>=10^5cfu/ml) *Proteus mirabilis* (>=10^5cfu/ml)	Levofloxacin	Eradicated	No
06004011	-	Levofloxacin	Eradicated	Yes
06012021	*E coli* (>=10^5cfu/ml) *Strep agalactiae* (>=10^5cfu/ml)	Levofloxacin	Eradicated	No
06018029	-	Levofloxacin	Eradicated	Yes
06020009	-	Levofloxacin	Eradicated	Yes
Enterococcus faecalis<10^5cfu/ml and >=10^3cfu/ml				
6008020	*E coli* <10^5cfu/ml and >=10^3cfu/ml	levofloxacin	Persisted	No
6015008	*E coli* <10^5cfu/ml and >=10^3cfu/ml	Levofloxacin	Eradicated	No
6015014	*E coli* <10^5cfu/ml and >=10^3cfu/ml *K oxytoca* <10^5cfu/ml and >=10^3cfu/ml	Ofloxacin	persisted	No
6015020	-	levofloxacin	Eradicated	No
6015029	-	ofloxacin	Eradicated	No
6015031	*E coli* <10^5cfu/ml and >=10^3cfu/ml	ofloxacin	Persisted	No
6016005	*E coli* <10^5cfu/ml and >=10^3cfu/ml	levofloxacin	Eradicated	No
6018021	*S agalactae* <10^5cfu/ml and >=10^3cfu/ml	levofloxacin	Persisted	No
6020022	-	levofloxacin	Eradicated	No
6023012	-	levofloxacin	Eradicated	No
6062015	*E coli* <10^5cfu/ml and >=10^3cfu/ml	ofloxacin	Eradicated	No
6065036	*E coli* <10^5cfu/ml and >=10^3cfu/ml	Levofloxacin	Eradicated	No

Only four patients with *Enterococcus* as a single admission pathogen in concentrations >=10^5 cfu/ml are reported. The organism was eradicated in all three who received levofloxacin, and persisted in the one patient who received ofloxacin. An additional four patients with *Enterococcus* as a single admission pathogen in concentrations <10^5 cfu/ml and >=10^3 cfu/ml are reported. These were regarded as unevaluable since concentrations of the organism were below the cutoff as stipulated in the protocol.

During infection with ***Staph saprophyticus***, the organism is commonly present in concentrations <10^5cfu/ml (CID1992;15:S218). In the reviewing this pathogen, all infections at colony counts >=10^3cfu/ml were evaluated.

Table 17 Summary of patients with *Staphylococcus saprophyticus* >=10^3cfu/ml)

Patient #	Colony count	Other organisms	Drug	Micro outcome	Reviewer evaluability
06004035	>=10^5cfu/ml	*Strep agalactiae* >=10^5cfu/ml	Levofloxacin	Eradicated	Yes
06010009	>=10^5cfu/ml	-	Levofloxacin	Eradicated	Yes
06012012	>=10^5cfu/ml	-	Levofloxacin	Eradicated	Yes
06020020	>=10^5cfu/ml	*Citrobacter freundii* >=10^5cfu/ml *enterobacter aerogenes* >=10^5cfu/ml	Levofloxacin	Eradicated	No
06022002	>=10^5cfu/ml	-	Levofloxacin	Presumed persisted	Yes
06022020	>=10^5cfu/ml	-	Levofloxacin	Presumed persisted	Yes
06022023	>=10^5cfu/ml	-	Ofloxacin	Presumed persisted	Yes
06023020	>=10^5cfu/ml	*E coli* >=10^5cfu/ml	Levofloxacin	Eradicated	Yes
06064004	>=10^5cfu/ml	-	Levofloxacin	Eradicated	Yes
06065003	>=10^5cfu/ml	-	Levofloxacin	Eradicated	Yes
06065015	>=10^5cfu/ml	-	Ofloxacin	Eradicated	Yes
06065029	>=10^5cfu/ml	-	Levofloxacin	Eradicated	Yes
06022028	>=10^3 and <10^5cfu/ml	-	Ofloxacin	Eradicated	Yes
06060032	>=10^3 and <10^5cfu/ml	-	Levofloxacin	Eradicated	Yes
06065031	>=10^3 and <10^5cfu/ml	*Proteus mirabilis* >=10^5cfu/ml	Ofloxacin	Eradicated	Yes
06004008	>=10^3 and <10^5cfu/ml	*E coli* >=10^5cfu/ml	Ofloxacin	Eradicated	Yes
06008030	>=10^3 and <10^5cfu/ml	-	Levofloxacin	Eradicated	Yes

Seventeen patients were identified with *Staphylococcus saprophyticus* at concentrations >=10^3cfu/ml on admission. Five of these cultures were polymicrobial. Given the strong association between *Staph saprophyticus* and a true UTI, only one of these five cultures with a copious growth of two other organisms was rejected. Among the remaining sixteen cases, the organism was eradicated in 9 of 11 levofloxacin recipients and presumed to persist in 2. Five infections with *staph saprophyticus* occurred in ofloxacin recipients. Four were eradicated and one was presumed to persist.

Table 18 Summary of patients with *Streptococcus agalactae* as a definite admission pathogen (>=10^5cfu/ml)

Patient #	Other organisms	Drug	Micro outcome
06004015	*E coli* >=10^5cfu/ml	Levofloxacin	Unknown
06004035	*Staph saprophyticus* >=10^5cfu/ml	Levofloxacin	Eradicated
06008031	-	Ofloxacin	Eradicated
06012021	*E coli*>=10^5cfu/ml *staph saprophyticus* >=10^5cfu/ml	Levofloxacin	Eradicated
06012028	*E coli* >=10^3 <10^5cfu/ml	Levofloxacin	Eradicated
06015003	*E coli* >=10^3 <10^5cfu/ml	Levofloxacin	Persisted
06020006	-	Ofloxacin	Eradicated
06023019	-	Ofloxacin	Persisted
06060010	-	Levofloxacin	Persisted
06060012	-	Levofloxacin	Persisted
06060015	-	Ofloxacin	Eradicated
06061009	-	Ofloxacin	Persisted

Three of the 12 infections with *strep agalactae* were polymicrobial. Among the remaining nine cases, the organism persisted in 3 of 4 cases treated with levofloxacin and 2 of 5 cases treated with ofloxacin.

Table 19 Summary of patients with *Proteus mirabilis*

Patient #	Other organisms	Drug	Micro outcome	Reviewer evaluability
Proteus mirabilis >=10^5cfu/ml				
06004003	*Strep faecalis* (>=10^5cfu/ml)	Ofloxacin	Eradicated	No
04004005	*E coli* (>=10^5cfu/ml) *E faecalis* (>=10^5cfu/ml)	Levofloxacin	Eradicated	No
06004028	*E coli* (<10^5cfu/ml and >=10^3cfu/ml)	Levofloxacin	Eradicated	Yes
06004030	*E coli* (<10^5cfu/ml and >=10^3cfu/ml)	Ofloxacin	Eradicated	Yes
06008009	*E coli* (<10^5cfu/ml and >=10^3cfu/ml)	Levofloxacin	Eradicated	Yes
06008012	*E coli* (<10^5cfu/ml and >=10^3cfu/ml)	Ofloxacin	Eradicated	Yes
06012019	-	Levofloxin	Eradicated	Yes
06015019	-	Ofloxacin	Eradicated	Yes
06016004	*E coli* (>=10^5cfu/ml)	Ofloxacin	Eradicated	No
06018036	-	Ofloxacin	Eradicated	Yes
06020008	-	Levofloxacin	Eradicated	Yes
06020012	*E coli* (>=10^5cfu/ml)	Levofloxacin	Eradicated	No
06020013	*Strep mutans* (>=10^5cfu/ml)	Ofloxacin	Eradicated	No
06020026	-	Ofloxacin	Eradicated	Yes
06060019	-	Ofloxacin	Eradicated	Yes
06060023	-	Ofloxacin	Eradicated	Yes
06062003	-	Ofloxacin	Eradicated	Yes
06063006	*E coli* (<10^5cfu/ml and >=10^3cfu/ml)	Levofloxacin	Eradicated	Yes
06065013	--	Ofloxacin	Eradicated	Yes
06065031	*E coli* (<10^5cfu/ml and >=10^3cfu/ml)	Ofloxacin	Eradicated	Yes
06019036	-	Ofloxacin	Eradicated	Yes
Proteus mirabilis <10^5cfu/ml and >=10^3cfu/ml				
6028018	-	levofloxacin	Eradicated	No

Five of 21 *Proteus mirabilis* infections contained multiple organisms at high concentrations and were designated unevaluable. Among the remaining 16 cases five were treated with levofloxacin and 11 with ofloxacin. The organism was eradicated in all cases.

Table 20 Summary of patients with *Klebsiella pneumoniae*

Patient #	Other organisms	Drug	Micro outcome	Reviewer evaluability
Klebsiella pneumoniae >=10^5 cfu/ml				
06001019	-	levofloxacin	Eradicated	Yes
06004001	-	ofloxacin	Eradicated	Yes
06004024	*E coli* (>=10^5 cfu/ml)	levofloxacin	Eradicated	Yes
06007012	-	levofloxacin	Eradicated	Yes
06007017	*Strep agalatae* (<10^5 cfu/ml and >=10^3 cfu/ml)	levofloxacin	Eradicated	Yes
06008028	-	ofloxacin	Eradicated	Yes
06016001	-	ofloxacin	Eradicated	Yes
06018008	*E coli* (>=10^5 cfu/ml)	levofloxacin	Eradicated	Yes
06018022	-	levofloxacin	Eradicated	Yes
06019030	-	ofloxacin	Eradicated	Yes
06020011	*E coli* (>=10^5 cfu/ml)	ofloxacin	Eradicated	Yes
06020029	-	levofloxacin	Persisted	Yes
06022004	-	ofloxacin	Eradicated	Yes
06061011	-	ofloxacin	Eradicated	Yes
06062010	-	levofloxacin	Eradicated	Yes
06062016	-	levofloxacin	Eradicated	Yes
06064011	*E coli* (>=10^5 cfu/ml)	levofloxacin	Eradicated	Yes
06065011	-	levofloxacin	Eradicated	Yes
06065035	-	ofloxacin	Eradicated	Yes
Klebsiella pneumoniae <10^5 cfu/ml and>=10^3 cfu/ml				
6008010	-	ofloxacin	Eradicated	No
6008024	-	ofloxacin	Eradicated	No

Four of 19 *Klebsiella pneumonia* infections contained more than one organism at concentrations >=10^5 cfu/ml. Given the strong association between *K Pneumoniae* and UTI, all the cases with admission colony counts >=10^5/ml were regarded as evaluable. Eleven were treated with levofloxacin and eight with ofloxacin. The organism persisted in one case treated with levofloxacin.

Table 21 Summary of microbiological eradication rates by pathogen for FDA selected microbiologically-evaluable subjects

	Levofloxacin	ofloxacin
Enterococcus faecalis	3/3	0/1
Klebsiella pneumonia	10/11	8/8
Proteus mirabilis	5/5	11/11
Staph saprophyticus	9/11	4/5

Table 22 Frequency of relapsing infection with specific pathogens, expressed as the number of relapses with each organism/total number of infections with that organism.

	Levofloxacin	Ofloxacin
E coli	7/127 (5.5%)	11/138 (8%)
K pneumonia	1/11 (9.1%)	0/8
E faecalis	0/10	0/3
Staph saprophyticus	1/8 (12.5%)	0/3
P mirabilis	0/7	1/14 (7.1%)
Strep agalactae	3/7 (42.9%)	2/8(25%)
Staph aureus	0/5	1/3 (33.3%)
E cloacae	2/4 (50%)	0/2

MO comment: Relapse rates were low for *E coli* but high among the small numbers of patients with *Strep agalactiae* and *E cloacae* infections, suggesting that a longer course of therapy might be helpful in these cases.

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Clinical results

The sponsor reported the following results based on the signs and symptoms of patients on admission and follow up. These findings were not supported by microbiological data.

Table 23 Clinical outcome among fully microbiologically evaluable population

	Levoflox (n=157)	Oflox (n=165)
Cured	86.6%	88.5%
Improved	11.5%	8.5%
Failed	1.9%	3%
Late relapse/new infection	9.6%	9.7%

Table 24 Clinical outcome among intent-to-treat population

	Levoflox (N=225)	Oflox (N=231)
Clinical success*	96.3%	94.3%
Relapse/new infection	8.4%	9.5%

* defined by sponsor to include symptomatic cure or improvement

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ON ORIGINAL

Table 25 Clinical outcome among modified intent-to-treat population

	Levoflox	Oflox
Clinical success	98.2%	96%

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The four tables below demonstrate the clinical and microbiological responses reported by the sponsor, each for infections with admission pathogen concentrations >=10^3cfu/ml and >=10^5cfu/ml, respectively

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Table 17a: Clinical Response Based on All Admission Pathogens for Subjects With Pathogens of Primary Interest[a]: Subjects Fully Evaluable for Microbiologic Efficacy (Protocol LOFBO-UTI-060)

Pathogen(s) from Urine Culture	No. (%) of Subjects									
	Levofloxacin					FLOXIN				
	N[b]	Cured		Improved	Failed	N[b]	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)
Streptococcus (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[c]	7	7	(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≥5 in either treatment group.

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

[c] Subject 15003 (levofloxacin) was erroneously excluded from the analyses (see Section 4.6.1). This subject should have been considered a clinical cure with microbiologic persistence.

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Table 17b: Clinical Response Based on Definite ($\geq 10^5$ cfu/mL) Admission Pathogens for Subjects With Pathogens of Primary Interest[a]: Subjects Fully Evaluable for Microbiologic Efficacy (Protocol LOFBO-UTI-060)

Pathogen(s) from Urine Culture	No. (%) of Subjects									
	Levofloxacin					FLOXIN				
	N[b]	Cured		Improved	Failed	N[b]	Cured		Improved	Failed
Escherichia coli	121	103	(85.1)	17 (14.0)	1 (0.8)	130	113	(86.9)	13 (10.0)	4 (3.1)
Klebsiella pneumoniae	9	9	(100.0)	0 (0.0)	0 (0.0)	8	8	(100.0)	0 (0.0)	0 (0.0)
Streptococcus (Enterococcus) faecalis	5	4	(80.0)	1 (20.0)	0 (0.0)	2	2	(100.0)	0 (0.0)	0 (0.0)
Staphylococcus saprophyticus	8	7	(87.5)	0 (0.0)	1 (12.5)	1	1	(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[c]	5	5	(100.0)	0 (0.0)	0 (0.0)	5	3	(60.0)	1 (20.0)	1 (20.0)

[a] N≥5 in either treatment group.

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

[c] Subject 15003 (levofloxacin) was erroneously excluded from the analyses (see Section 4.6.1). This subject should have been considered a clinical cure with microbiologic persistence.

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Table 12a: Microbiologic Eradication Rates Based on All Admission Pathogens Summarized by Pathogen Category and Pathogen: Subjects Fully Evaluable for Microbiologic Efficacy (Protocol LOFBO-UTI-060)

Urine Cultures:	Levofloxacin		FLOXIN		
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]	95% CI[b]
Pathogen Category					
gram positive aerobic pathogens	35	31 (88.6)	19	14 (73.7)	(-40.0, 10.2)
gram negative aerobic pathogens	155	152 (98.1)	168	161 (95.8)	(-6.3, 1.8)
Total by pathogen	190	183 (96.3)	187	175 (93.6)	(-7.4, 2.0)
Total by subject[c]	157	151 (96.2)	165	153 (92.7)	(-8.7, 1.8)
Pathogen[d]					
Escherichia coli	127	125 (98.4)	138	131 (94.9)	(-8.1, 1.1)
Klebsiella pneumoniae	11	10 (90.9)	8	8 (100.0)	
Streptococcus (Enterococcus) faecalis	10	9 (90.0)	3	1 (33.3)	
Staphylococcus saprophyticus	8	8(100.0)	3	3 (100.0)	
Proteus mirabilis	7	7(100.0)	14	14 (100.0)	
Streptococcus agalactiae[e]	7	5 (71.4)	8	5 (62.5)	
Staphylococcus aureus	5	5(100.0)	3	3 (100.0)	

[a] Numbers shown in parentheses are percentages for that category.

[b] Two-sided 95% confidence interval around the difference (FLOXIN minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.

[c] Eradication of all pathogens isolated for a subject at admission.

[d] N≥5 for either treatment group. Multiple strains are counted separately.

[e] Subject 15003 (levofloxacin) was erroneously excluded from the analyses (see Section 4.6.1). This subject should have been counted as a clinical cure with microbiologic persistence, thus the eradication rate for *S. agalactiae* should have been 62.5%.

Table 12b: Microbiologic Eradication Rates Based on Definite ($\geq 10^5$ cfu/mL) Admission Pathogens Summarized by Pathogen Category and Pathogen: Subjects Fully Evaluable for Microbiologic Efficacy (Protocol LOFBO-UTI-060)

Urine Cultures:	Levofloxacin		FLOXIN		
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]	95% CI[b]
Pathogen Category					
gram positive aerobic pathogens	23	20 (87.0)	10	7 (70.0)	(-53.5, 19.6)
gram negative aerobic pathogens	146	143 (97.9)	164	158 (96.3)	(-5.6, 2.4)
Total by pathogen	169	163 (96.4)	174	165 (94.8)	(-6.2, 3.0)
Total by subject[c]	157	151 (96.2)	165	156[d] (94.5)	(-6.5, 3.3)
Pathogen[e]					
Escherichia coli	121	119 (98.3)	134	128 (95.5)	(-7.4, 1.8)
Klebsiella pneumoniae	9	8 (88.9)	8	8 (100.0)	
Streptococcus (Enterococcus) faecalis	5	5(100.0)	2	1 (50.0)	
Staphylococcus saprophyticus	8	8(100.0)	1	1 (100.0)	
Proteus mirabilis	7	7(100.0)	14	14 (100.0)	
Streptococcus agalactiae[f]	5	3 (60.0)	5	3 (60.0)	

[a] Numbers shown in parentheses are percentages for that category.

[b] Two-sided 95% confidence interval around the difference (FLOXIN minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.

[c] Eradication of all definite pathogens isolated for a subject at admission.

[d] Three FLOXIN-treated subjects (4020, 8012, and 65027) who are included in this analysis as having an infection outcome of eradicated are considered as having persistence of their infection when both definite and possible admission pathogens are considered (as in Table 12a and the CANDA data base).

[e] N≥5 for either treatment group. Multiple strains are counted separately.

[f] Subject 15003 (levofloxacin) was erroneously excluded from the analyses (see Section 4.6.1). This subject should have been counted as a clinical cure with microbiologic persistence, thus the eradication rate for *S. agalactiae* should have been 50%.

MO comment: Clinical responses (17a and 17b) for a number of pathogens appeared worse than microbiological responses (tables 12a and 12b). This corroborated the admission findings that many symptomatic patients had negative urine cultures. As such, clinical symptoms appear to be of poor specificity in the evaluation of these patients with uncomplicated UTI.

As anticipated, a cutoff of 10^5cfu/ml tended to eliminate several cases infected with mainly gram positive pathogens including *Enterococcus faecalis*, *Staph saprophyticus*, *Strep agalactiae* and 8 cases of *Staph aureus*. While the activity of levofloxacin against these organisms appears good, the statistical strength of these claims is limited by small patient numbers even in the group with less stringent colony counts

Safety:
All subjects except 3 ofloxacin recipients lost to follow up, were evaluated for safety. Adverse events were recorded in 30.2% of the levofloxacin recipients and 32.8% of the ofloxacin recipients. Most were gastrointestinal, CNS, or "whole body". Headache and nausea were the most common individual symptoms.

Treatment emergent adverse events were considered probably or definitely related to study drug in 3.4% of levofloxacin treated subjects and 7.5% of ofloxacin treated subjects.
Fungal infections, back pain and nausea were more frequent in the levofloxacin recipients.

Eleven serious adverse events were reported in levofloxacin recipients and 15 in ofloxacin recipients. Most were not related to the study drug. There were no deaths. Only one levofloxacin treated subject had a serious adverse event that was considered drug related, recorded as nausea. Six ofloxacin treated patients had severe adverse events considered study drug related. They included numbness (1) headache (1) bad dreams (1) chest pain (1) and abdominal pain (2).

Table 4: Incidence of Frequently Reported (≥2%)[a] Adverse Events: Summarized by Body System and Primary Term: Subjects Evaluable for Safety (Protocol LOHBO-UTI-060)

	No. (%) of Subjects			
	Levofloxacin (N=298)		FLOXIN (N=295)	
Body System/Primary Term				
All body systems[b]	90	(30.2)	96	(32.8)
Skin and appendages disorders				
Pruritus genital	5	(1.7)	6	(2.0)
Central & peripheral nervous system disorders				
Dizziness	0	(0.0)	6	(2.0)
Headache	15	(5.0)	23	(7.8)
Psychiatric disorders				
Dreaming abnormal[b]	1	(2.9)	3	(10.0)
Insomnia[b]	2	(5.7)	2	(6.7)
Paroniria[b]	0	(0.0)	1	(3.3)
Gastro-intestinal system disorders				
Abdominal pain	9	(3.0)	14	(4.8)
Diarrhea	6	(2.0)	9	(3.1)
Dyspepsia	3	(1.0)	6	(2.0)
Nausea	11	(3.7)	9	(3.1)
Respiratory system disorders				
Sinusitis	4	(1.3)	6	(2.0)
Body as a whole - general disorders				
Back pain	9	(3.0)	5	(1.7)
Resistance mechanism disorders				
Infection fungal	9	(3.0)	3	(1.0)

[a] Primary term reported by ≥2.0% of subjects in either treatment group.
[b] Sleep disorder event percentages calculated from the total number of subjects in each treatment group who did not participate in the IVR Program, or who discontinued due to a sleep disorder adverse event. The levofloxacin denominator was 35, and the FLOXIN denominator was 30.

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Four subjects on ofloxacin discontinued the drug prematurely because of hypoasthesia and vomiting, abnormal dreams, abdominal pain, chest pain, "heart disorder" and increased sweating. No premature discontinuation of drug for adverse effects was recorded for levofloxacin recipients.

Laboratory tests:
Hypoglycemia in (1.8% of the ofloxacin treated patients) and lymphopenia (in 1.1% of the levofloxacin treated patients) accounted for most of the laboratory abnormalities recorded. Lymphocyte counts at their nadir were 0.68, 0.86 and 0.87 X 10^3 /µl in the levofloxacin treated patients and 0.73 and 0.83 X 10^3 /µl in the ofloxacin treated patients. All were observed between study day 8 and day 15.

Table 5: Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Protocol LOFBCUTI-0600)

Laboratory Test	Levofloxacin Proportion[a]	Levofloxacin %	FLOXIN Proportion[a]	FLOXIN %
Blood Chemistry				
Decreased Glucose (mg/dL)	1/287	0.3	5/284	1.8
Elevated Sodium (mEq/L)	1/288	0.3	0/285	0.0
Elevated Bilirubin (mg/dL)	0/286	0.0	1/281	0.4
Hematology				
Decreased Hemoglobin (g/dL)	1/284	0.4	0/283	0.0
Decreased Lymphocytes ($1x10^3/\mu L$)	3/284	1.1	2/283	0.7

[a] Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable (i.e., admission and postadmission data available) for that analyte.

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Further review of safety data across levofloxacin trials:

Safety data were reviewed from 17 phase three studies of levofloxacin incorporating 3865 subjects. The demographic characteristics in 2879 levofloxacin recipients and 2885 comparator recipients in actively controlled trials were similar. Oral levofloxacin was administered for a mean of 9.3 days per patient. 37.9% of levofloxacin treated patients and 40.2% of subjects treated with control drugs reported adverse events, predominantly gastrointestinal and CNS. Severe events were reported in 4.4% of 2848 levofloxacin recipients and 5.1% of control drug recipients. Adverse events in the present study were similar to those in previous phase 3 studies of levofloxacin. Headache and insomnia were most frequent (>5%). Among ofloxacin recipients, abnormal dreams, insomnia and headache were most frequent (>5%). Of the levofloxacin recipients 5.6% experienced adverse events attributed to the drug compared with 7.9 control drug recipients. Less common drug related events were diarrhoea (2.8% of control subjects), nausea (1.8% of control subjects and 1.5% of levofloxacin treated subjects) and vaginitis (1.2% of control subjects). Reports of markedly abnormal analytes occurred in 1.8%of levofloxacin recipients and 1.9% of controls in active controlled studies.

Other labeling changes: The sponsor has provided a revised paragraph in the label under ADVERSE REACTIONS reflecting the updated incidence rates for each event. The changes are minor and do not raise any new safety concerns. Several previously unlisted adverse events have been added that occurred at low frequencies. These include: coughing, ear disorder (not otherwise specified), fungal infection, agitation, arthrosis, asthenia, atrial fibrillation, carcinoma, cholelithiasis, conjunctivitis, dysphagia, ejaculation failure, face edema, gastroenteritis, genital moniliasis, hematuria, haemoptysis, hyperglycaemia, hyperkalaemia, hyperkinesia, hypertonia, hypoaesthesia, hypokalaemia, hypoxia, impotence, involuntary muscle contractions, malaise, nervousness, palpitation, paraesthesia, parosmia, phlebitis, pleural effusion, respiratory insufficiency, rigors, skin exfoliation, skin ulceration, substernal chest pain, supraventricular tachycardia, synovitis, ventricular fibrillation, withdrawal syndrome. Minor changes in wording have been made in the CONTRAINDICATIONS section clarifying the fact that certain adverse events seen with quinolones in general have occurred during the use of levofloxacin as well.
These changes are acceptable to the FDA.

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MO main conclusions:
The selection of the comparator "ofloxacin", in the three day regimen described is appropriate for the evaluation of uncomplicated UTI's caused by *E coli* and *Klebsiella pneumoniae*. For other organisms including *Proteus mirabilis*, *Citrobacter diversus* and *Pseudomonas aeruginosa*, ofloxacin is approved for use as a seven day course. Ofloxacin is not approved for the treatment of uncomplicated UTI caused by *Staphylococcus saprophyticus* or *Enterococcus faecalis*, though comparative data for these organisms are presented in this application and approval is sought for short course levofloxacin in the treatments of uncomplicated UTI due to these organisms.

The data provided support for clinical and microbiological equivalence in the efficacy of levofloxacin 250mg daily for three days and ofloxacin 200 mg bd for three days in the treatment of uncomplicated UTI. This indication would apply to young non-pregnant women with a history of symptoms less than seven days, not previously on antimicrobials with no anatomic abnormalities of the urinary tract and no recent urinary tract instrumentation, who are infected with susceptible organisms. The resulting microbiological

cure rate with levofloxacin was 96%, 5-9 days after completion of the antibiotic course. The relapse rate 4-6 weeks later was 14.6%.

The use of intravenous levofloxacin has not been examined in the context of uncomplicated UTI. While it is likely to be effective in the treatment of uncomplicated UTI's, it would seldom be practical to treat uncomplicated UTI with this IV regimen. It is suggested that both these issues be reflected in the label of the parenteral product.

Claims for efficacy against specific pathogens were evaluated. The bulk of data were obtained from patients infected with *E coli* (127/157 cases), clearly supporting the efficacy of the described regimen against this organism. According to the population evaluated by the FDA, insufficient numbers of cases infected with *E faecalis* (3 cases) or *Proteus mirabilis* (5 cases) were described in this study to provide independent support to these efficacy claims, despite in vitro MIC data and clinical data from a previous NDA (studies K91-058 and L91-059) supporting the use of levofloxacin for ten days in complicated UTI's with these organisms. Justification of these claims technically requires that at a minimum, 10% (or 10 cases whichever is the greater) of cases meeting the clinically and microbiologically evaluable criteria for each pathogen should be reported (FDA anti-infective drug advisory committee meeting, July 1998). Acceptable clinical data was supplied to support the use of the study regimen for uncomplicated UTI due to *Klebsiella pneumoniae* and *Staphylococcus saprophyticus*. Ten of 11 infections with *K pneumoniae* and 9 of 11 infections with *Staph saprophyticus* were microbiologically eradicated with levofloxacin.

Safety: The present study did not alter the safety experience obtained previously from 2741 patients in phase 3 studies. Further, adverse events were generally less common in levofloxacin recipients than ofloxacin recipients. The most notable were headache, nausea and lymphopenia. Only one patient in the present study had an event of "marked severity" that was probably drug related, namely nausea. A three day course of levofloxacin appeared safe over a follow-up period of up to 8 weeks, in this population of young women.

Additional correspondence/telecons with Sponsor:
During a telecon on 12/10/1998 the sponsor was appraised of the reviewed data with regard to efficacy claims for individual organisms. The sponsor was not in possession of additional data to support efficacy claims against *P mirabilis* and *E faecalis*, and agreed to forward a revision to the proposed label where these organisms would be omitted from the "indications and usage" section.

Specific labeling recommendations:

Under indications and usage:

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

Under dosing and administration:

Patients with Normal Renal Function:

Infection*	Unit Dose	Freq.	Duration	Daily Dose
Acute Bacterial Exacerbation of	500 mg	q24h	7 days	500 mg
Chronic Bronchitis				
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg

Acute Maxillary Sinusitis	500 mg	q24h	10-14 days	500 mg
Uncomplicated SSSI	500 mg	q24h	7-10 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.)**

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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

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Under Adverse Reactions: (The FDA has not recommended any changes to the proposed labeling of this section)

ADVERSE REACTIONS

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The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.2%. Among patients receiving levofloxacin therapy, 3.4% discontinued levofloxacin therapy due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:
nausea 1.3%, diarrhea 1.1%, vaginitis 0.7%, pruritus 0.5%, abdominal pain 0.4%, dizziness 0.4%, flatulence 0.4%, rash 0.4%, dyspepsia 0.3%, genital moniliasis 0.3%, insomnia 0.3%, taste perversion 0.2%, vomiting 0.2%, anorexia 0.1%, anxiety 0.1%, constipation 0.1%, edema 0.1%, fatigue 0.1%, fungal infection 0.1%, headache 0.1%, increased sweating 0.1%, leukorrhea 0.1%, malaise 0.1%, nervousness 0.1%, sleep disorders 0.1%, tremor 0.1%, urticaria 0.1%.

In clinical trials, the following events occurred in >3% of patients, regardless of drug relationship:
nausea 7.1%, headache 6.4%, diarrhea 5.6%, insomnia 4.0%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:
constipation 2.9%, dizziness 2.9%, abdominal pain 2.6%, dyspepsia 2.5%, vomiting 2.2%, rash 1.7%, flatulence 1.6%, vaginitis 1.6%, pruritus 1.5%, fatigue 1.3%, back pain 1.2%, pain 1.2%, chest pain 1.1%, pharyngitis 1.1%, rhinitis 1.1%, taste perversion 1.0%.

In clinical trials, the following events occurred in 0.5 to less than 1% of patients, regardless of drug relationship:

anorexia, anxiety, arthralgia, coughing, dry mouth, dyspnea, ear disorder (not otherwise specified), edema, fever, fungal infection, genital pruritus, increased sweating, skin disorder, somnolence.

In clinical trials, the following events, of potential medical importance, occurred at a rate of less than 0.5% regardless of drug relationship:
abnormal coordination, abnormal dreaming, abnormal hepatic function, abnormal platelets, abnormal renal function, abnormal vision, acute renal failure, aggravated diabetes mellitus, aggressive reaction, agitation, anemia, angina pectoris, ARDS, arrhythmia, arthritis, arthrosis, asthenia, asthma, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure, carcinoma, cerebrovascular disorder, cholelithiasis, circulatory failure, coma, confusion, conjunctivitis, convulsions (seizures), coronary thrombosis, dehydration, delirium, depression, diplopia, dysphagia, ejaculation failure, embolism (blood clot), emotional lability, epistaxis, erythema nodosum, face edema, gastroenteritis, genital moniliasis, G.I. hemorrhage, granulocytopenia, haematuria, haemoptysis, hallucination, heart block, hepatic coma, hyperglycaemia, hyperkalaemia, hyperkinesia, hypertension, hypertonia, hypoaesthesia, hypoglycemia, hypokalaemia, hypotension, hypoxia, impaired concentration, impotence, increased LDH, involuntary muscle contractions, jaundice, leukocytosis, leukopenia, lymphadenopathy, malaise, manic reaction, mental deficiency, muscle weakness, myalgia, myocardial infarction, nervousness, palpitation, pancreatitis, paraesthesia, paralysis, paranoia, parosmia, phlebitis, pleural effusion, postural hypotension, pseudomembranous colitis, purpura, respiratory insufficiency, rhabdomyolysis, rigors, skin exfoliation, skin ulceration, sleep disorders, speech disorder, stupor, substernal chest pain, supraventricular tachycardia, syncope, synovitis, tachycardia, tendinitis, thrombocytopenia, tinnitus, tongue edema, tremor, urticaria, ventricular fibrillation, vertigo, weight decrease, WBC abnormal (not otherwise specified), withdrawal syndrome.

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 laboratory abnormalities appeared _____ 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
Hematology: decreased lymphocytes

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, Stevens-Johnson Syndrome, tendon rupture, vasodilation.

/S/

Leonard V Sacks, M.D.
Medical officer, DSPIDP

Concurrence
HFD590/MTL/HopkinsR

CC:
NDA 20-634
HFD-590/DivDir/GoldbergerM
HFD-590/MTL/HopkinsR
HFD-590/MO/SacksL
HFD-590/PM/AndersonR
HFD-590/Micro/DioneP
HFD590/Biostat/SillimanN

/S/ 12/11/08
/S/ 12/11/08