CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

CHEMISTRY REVIEW(S)

DEC 8 1998

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

3. NAME AND ADDRESS OF APPLICANT: *(City and State)*
The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

4. AF NUMBER:

5. SUPPLEMENT(S):

NUMBER(S):	DATE(S):
SE1-004	June 4, 1998
SE1-004/BC	October 28, 1998

6. NAME OF DRUG:
LEVAQUIN® Tablets

7. NONPROPRIETARY NAME:
Levofloxacin Tablets

8. SUPPLEMENT(S) PROVIDES FOR:
New indication for uncomplicated urinary tract infections.

9. AMENDMENTS/REPORTS:

10. PHARMACOLOGICAL CATEGORY:
Antibacterial (Synthetic): Quinolone

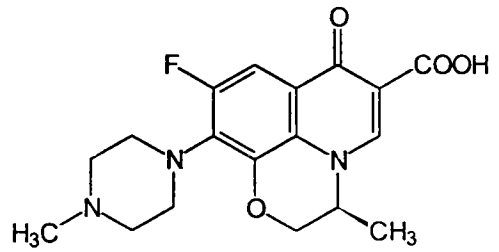
11. HOW DISPENSED:
[X] Rx [ ]OTC

12. RELATED IND/NDA/DMF(S):

13. DOSAGE FORM(S):
Tablets

14. POTENCY(IES):
250 and 500 mg

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



1/2 H_2O

16. MEMORANDA:

APPEARS THIS WAY
ON ORIGINAL

17. COMMENTS: This supplemental new drug application 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. There are no CMC issues other than Environmental Assessment. The information was forwarded to N. Sager for consult on June 19, 1998. The initial EA was found to be deficient and no FONSI was issued. R.W. Johnson filed additional information (BC amendment) which was reviewed by N. Sager. A FONSI was issued and the consult completed on December 2, 1998.

18. CONCLUSIONS AND RECOMMENDATIONS: A FONSI has been issued and there are no other CMC issues connected with this application. The supplement may be approved from a CMC perspective.

19. REVIEWER:	SIGNATURE:	DATE COMPLETED:
Gene W. Holbert, Ph.D.	/S/	12-8-98
20. CONCURRENCE:		
Norman R. Schmuff, Ph.D.	/S/	12/8/98

DISTRIBUTION:						
	X	Original NDA	X	HFD-590: NSchmuff	X	HFD-590: RAnderson
	X	Division File HFD-590	X	HFD-590: GHolbert	X	HFD-830: CChen

DEC 8 1998

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION: HFD-590	2. NDA NUMBER: 20-635

3. NAME AND ADDRESS OF APPLICANT: *(City and State)*
The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

APPEARS THIS WAY
ON ORIGINAL

4. AF NUMBER:

5. SUPPLEMENT(S):

NUMBER(S):	DATE(S):
SE1-003	June 4, 1998
SE1-003/BC	October 28, 1998

6. NAME OF DRUG:
LEVAQUIN® Injection

7. NONPROPRIETARY NAME:
Levofloxacin Injection

8. SUPPLEMENT(S) PROVIDES FOR:
New indication for uncomplicated urinary tract infections.

9. AMENDMENTS/REPORTS:
APPEARS THIS WAY
ON ORIGINAL

10. PHARMACOLOGICAL CATEGORY:
Antibacterial (Synthetic): Quinolone

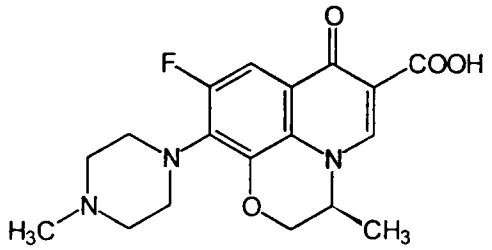
11. HOW DISPENSED:
[X] Rx [ ]OTC

12. RELATED IND/NDA/DMF(S):

13. DOSAGE FORM(S):
Injection

14. POTENCY(IES):
5 and 25 mg/mL

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



1/2 H_2O

16. MEMORANDA:

APPEARS THIS WAY
ON ORIGINAL

17. COMMENTS: This supplemental new drug application 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. There are no CMC issues other than Environmental Assessment. The information was forwarded to N. Sager for consult on June 19, 1998. The initial EA was found to be deficient and no FONSI was issued. R.W. Johnson filed additional information (BC amendment) which was reviewed by N. Sager. A FONSI was issued and the consult completed on December 2, 1998.

18. CONCLUSIONS AND RECOMMENDATIONS: A FONSI has been issued and there are no other CMC issues connected with this application. The supplement may be approved from a CMC perspective.

19. REVIEWER:	SIGNATURE:	DATE COMPLETED:
Gene W. Holbert, Ph.D.	/S/	12-8-98
20. CONCURRENCE:		
Norman R. Schmuff, Ph.D.	/S/	12/8/98

DISTRIBUTION:						
	X	Original NDA	X	HFD-590: NSchmuff	X	HFD-590: RAnderson
	X	Division File HFD-590	X	HFD-590: GHolbert	X	HFD-830: CChen

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-634/S-004 and 20-635/S-003

LEVAQUIN® (levofloxacin) Tablets and Injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of their supplemental new drug applications for LEVAQUIN® (levofloxacin) Tablets and Injection, The R.W. Johnson Pharmaceutical Research Institute has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product. Levofloxacin is a [redacted] drug which is currently approved for treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinustitis, complicated urinary tract infections, acute pyelonephritis, and uncomplicated skin and skin structure infections. These supplemental applications are requesting approval of the product for use in the treatment of uncomplicated urinary tract infection.

Levofloxacin may enter both the aquatic and terrestrial environment from patient use and disposal and is expected to rapidly degrade when exposed to light. Although degradation mechanisms have been demonstrated for the aquatic and terrestrial environment, the toxicity of levofloxacin to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

12/1/98
DATE

/S/
PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

12-1-98
DATE

/S/
CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

STATISTICAL REVIEW(S)

Anderson

DEC 2 1998

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-634/S-004 and 20-635/S-003
Name of Drug:	LEVAQUIN (levofloxacin) tablets and I.V.
Applicant:	R.W. Johnson PRI
Indication(s):	Uncomplicated urinary tract infection.
Documents Reviewed:	Volumes 1.1, 1.20 - 1.34, and electronic submission.
Review Type:	Clinical.
Statistical Reviewer:	Nancy Paul Silliman, Ph.D., HFD-725
Medical Officer:	Leonard Sacks, MD, HFD-590
Project Manager:	Robin Anderson, HFD-590

I. INTRODUCTION

Ofloxacin (FLOXIN ®) is a racemic mixture of D- and L-isomers. The antibacterial activity of ofloxacin resides primarily in the L-isomer, levofloxacin (LEVAQUIN ®). Levofloxacin has been approved by the U.S. Food and Drug Administration (FDA) in both oral and intravenous formulations for various indications including complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa* and acute pyelonephritis (mild to moderate) caused by *Escherichia coli.*

The sponsor is requesting that levofloxacin in both oral and intravenous formulations also be approved for uncomplicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Staphylococcus saprophyticus* (note: levofloxacin is approved for use against the first four organisms in complicated urinary tract infections (UTI); *Staphylococcus saprophyticus* is not included in the currently approved indication for complicated UTI.) To support this request, the sponsor has conducted one multicenter, double-blind, randomized study of oral levofloxacin versus oral ofloxacin in the treatment of uncomplicated UTI in women. In this study, patients were randomized in a 1:1 ratio to receive either 250 mg levofloxacin once daily for three days or 200 mg ofloxacin taken orally twice daily for three days. (Note: 200 mg ofloxacin taken orally twice daily for seven days is an approved regimen for the treatment of uncomplicated

urinary tract infections; 200 mg ofloxacin taken orally twice daily for three days is not an approved regimen for the treatment of uncomplicated UTI.)

Therapeutic equivalence of levofloxacin to ofloxacin was demonstrated for the primary efficacy endpoint, microbiologic response posttherapy in subjects fully evaluable for microbiologic efficacy, using a delta of 10%. At this timepoint, 5-9 days after completion of study drug, the infection eradication rate by subject was 96.2% with levofloxacin and 92.7% with ofloxacin. The 95% exact confidence interval for the difference in eradication rates, levofloxacin minus ofloxacin, is (-3.1%, 10.8%). (Note: In their submission, the sponsor uses the normal approximation to the binomial distribution with a continuity correction to calculate confidence intervals. Since the rates found in this study are generally high, i.e., in the 90's, this reviewer uses the exact method to calculate confidence limits.)

Note that even if we assumed that 200 mg ofloxacin taken orally twice daily for seven days would achieve a 100% eradication rate in the population studied, levofloxacin would still be able to show therapeutic equivalence to ofloxacin using a delta of 10%. The 95% confidence interval for the difference between levofloxacin (96.2%) and ofloxacin (100%, under the worst-case [for levofloxacin] assumption that all patients would have been eradicated had they been treated with ofloxacin for 7 days instead of the 3 days given in this study) would be (-9.6%, 0.7%).

Adverse event rates were generally consistent between levofloxacin and ofloxacin.

Section II summarizes results in more detail from the one study that has been submitted. Section III provides some conclusions.

II. STUDY OF LEVAQUIN VS. FLOXIN IN UNCOMPLICATED UTI

Reviewer's Note: Much of what is reported in this section is taken directly from the sponsor's application. Reviewer notes will be highlighted in italics.

This was a randomized, double-blind, active-control, multicenter (24 centers) study designed to evaluate levofloxacin in the treatment of uncomplicated UTI. The study was conducted in the United States. Approximately 600 female subjects between the ages of 18 and 55 years with a diagnosis of uncomplicated UTI with pyuria and presumed bacteriuria accompanied by either urinary urgency, frequency, or dysuria were to be enrolled. It was expected that this would ensure microbiologically evaluable data from a minimum of 300 subjects (150 subjects in each of two treatment groups) with an admission colony count of $>10^5$ cfu/mL. Subjects were to be randomly assigned to one of two treatment groups in a 1:1 ratio according to a randomization schedule prepared by the sponsor. Subjects received either 250 mg levofloxacin orally once daily for three days or 200 mg ofloxacin orally twice daily for three days.

Reviewer's Note: 200 mg ofloxacin taken orally twice daily for three days is not an approved regimen for the treatment of uncomplicated UTI. An approved regimen for ofloxacin for the treatment of uncomplicated urinary tract infections is 200 mg taken orally twice daily for seven days.

Levofloxacin 250 mg was supplied in capsules containing a terra cotta pink, film-coated, debossed, modified rectangular 250 mg levofloxacin tablet. ofloxacin 200 mg was supplied in capsules containing light yellow, oval, film-coated 200 mg ofloxacin tablets. To maintain the blinding of both levofloxacin and ofloxacin, the tablets were placed inside a blue opaque capsule, size "00." Each subject was to receive one capsule twice a day (six capsules in three days). Subjects receiving levofloxacin received active drug in doses 1, 3, and 5 and a placebo agent in doses 2, 4, and 6. Drug was packaged in blistercards with three days of dosing (two capsules b.i.d.) on each card, a total of six capsules per blistercard. Each blistercard was packed in individual cartons. The doses were numbered and were to be taken sequentially from one to six.

The randomization schedule was randomly generated in blocks of six and stratified within study centers, assigning subjects in equal numbers to receive either levofloxacin or ofloxacin.

Reviewer's Note: The sponsor's primary analysis does not adjust for center. However, response rates are examined across centers to see if any differences exist.

The **primary efficacy variable, microbiologic response to treatment posttherapy**, was evaluated in terms of both pathogen and infection eradication rates. Each organism isolated was assigned a pathogenic classification according to the following criteria: definite admission pathogen ($\geq 10^5$ cfu/mL at baseline), possible admission pathogen ($\geq 10^3$ but $<10^5$ cfu/mL at baseline), superinfector, colonizer, definite new infector, possible new infector, definite reinfector, and possible reinfector. Microbiologic response was assessed at both posttherapy (5-9 days after completion of study drug; this was the primary timepoint) and poststudy (4-6 weeks after completion of study drug; only patients who were clinical cures or improvements at posttherapy were seen for this visit). Microbiologic response by pathogen at posttherapy was assessed as either eradicated ($<10^3$ cfu/mL), persisted ($\geq 10^3$ cfu/mL), presumed persisted, persisted with acquisition of resistance, or unknown. Microbiologic response by subject was assessed at posttherapy as either eradicated (all admission pathogens eradicated), persisted, or unknown. At poststudy, microbiologic response by pathogen was assessed as either eradicated, persisted, microbiologic relapse, presumed microbiologic relapse, or unknown; microbiologic response by subject was assessed as either eradicated, persisted, microbiologic relapse, or unknown.

Reviewer's Note: Several working definitions were developed by the sponsor as part of the analyses that were not included in the protocol. Most of these are straightforward (e.g., defining a "definite reinfector" as an organism isolated from an admission urine culture at $\geq 10^5$ cfu/mL, with presumed or documented eradication at the posttherapy visit, isolated after the posttherapy visit, and assessed as a microbiologic relapse at the

poststudy visit). However, one definition that causes more concern is the following. When a pathogen was identified poststudy at ≥10^3 cfu/mL but <10^5 cfu/mL, if the subject was asymptomatic based on the clinical outcome at poststudy, effective concomitant therapy was not administered, and the colony count was lower than that found at baseline, the pathogen was given a response of eradicated. This reviewer examined the number of pathogens assigned a response of eradicated poststudy using this definition, and reassessed relapse rates using the original definition. The revised relapse rates were similar for the two treatment groups (see below).

Clinical response was also assessed at both posttherapy (cure, improved, failure, unable to evaluate) and poststudy (cure, clinical relapse/new infection, unable to evaluate).

Several analysis groups were considered. The **primary analysis group** was those patients considered **fully evaluable for microbiologic efficacy** (note: clinical response was also assessed primarily in this group). Patients that were classified in any of the following categories were excluded from this primary analysis group:

- not evaluable for safety (did not take at least one dose of study drug or had no postadmission safety data available);
- absence of bacteriologically proven infection (i.e., no definite admission pathogen isolated, defined as pathogen in admission culture at ≥10^5 cfu/mL);
- insufficient course of therapy (subject did not take the full course of therapy; however, a subject judged as a clinical failure after receiving study drug for at least 48 hours, or four doses, was to be considered evaluable);
- effective systemic antimicrobial therapy taken at any time between the admission culture through the posttherapy culture, unless judged to be a clinical failure;
- inappropriate bacteriologic cultures (admission culture >48 hours prior to the start of therapy or any time after the start of therapy; posttherapy culture not between 5 to 12 days posttherapy; posttherapy urine culture results not available. If a subject was a clinical failure and no valid posttherapy culture was obtained, the subject is evaluable and the pathogens isolated at admission are presumed to persist);
- lost to follow-up but provided safety information, or other protocol violation (e.g., subject reenters the study).

Other analysis groups that were examined include:

- **Intent-to-Treat (ITT):** All subjects enrolled according to randomization, regardless of whether or not an admission pathogen was isolated.
- **Modified Intent-to-Treat Subjects with an Admission Pathogen:** Those subjects in the intent-to-treat population who had a definite pathogen (≥10^5 cfu/mL) isolated at admission.
- **Fully Microbiologically Evaluable from High Enrolling Centers:** All fully microbiologically evaluable subjects enrolled at study centers with a total of at least 10 fully microbiologically evaluable subjects per treatment group.
- **Possibly Microbiologically Evaluable:** Subjects with signs and symptoms of acute uncomplicated UTI according to the protocol-specified evaluability criteria described previously, and with a possible admission pathogen identified in the admission culture (≥10^3 cfu/mL but <10^5 cfu/mL).

Three of the five efficacy analysis populations described above (subjects fully evaluable for microbiologic efficacy, modified intent-to-treat subjects with an admission pathogen, and subjects fully microbiologically evaluable from high enrolling centers) by definition include subjects with a definite admission pathogen ($\geq 10^5$ cfu/mL). For any given subject in these three populations, any definite admission pathogen(s), and, if present, any possible admission pathogen(s) ($\geq 10^3$ cfu/mL and $<10^5$ cfu/mL) were included in the by-pathogen efficacy analyses. The by-subject microbiologic response was determined by the pathogen response of all admission pathogens, definite and possible. In addition to these analyses, pathogen and infection eradication rates were provided for the primary analysis population of fully microbiologically evaluable subjects using only the definite admission pathogen(s) ($\geq 10^5$ cfu/mL) for each subject. Clinical response rates for pathogens of interest (N≥5 in either treatment group) using only definite admission pathogens ($\geq 10^5$ cfu/mL) were also determined for this population.

Safety evaluations included the incidence of treatment-emergent adverse events; review of laboratory tests of hematology, blood chemistry, and urinalysis; and evaluation of physical examinations including vital signs.

Results

Five hundred ninety-four subjects were enrolled in this study at 23 centers in the U.S. (Dr. Kalet's center did not enroll any subjects). The intent-to-treat population included all 594 subjects; 298 subjects who were randomly assigned to the levofloxacin treatment group, and 296 subjects who were randomly assigned to the ofloxacin treatment group. Of the 298 levofloxacin subjects enrolled, 3 withdrew from the study and 2 had unknown completion/withdrawal information (both patients took 3 days of study drug and then were lost to follow-up). Of the 296 ofloxacin patients, 5 withdrew from the study and 3 had unknown completion/withdrawal information (each of the three patients was lost to follow-up before the first telephone contact and hence no information, either efficacy or safety, is available on these 3 patients). Reasons for premature withdrawal from the study are summarized in Table 1 below.

Reviewer's Note: Withdrawal rates were similar between the two treatment arms.

Table 1. Study Completion/Withdrawal Information: Intent-to-Treat Population

Reason for Premature Withdrawal	Levofloxacin (N=298) No.	(%)[a]	FLOXIN (N=296) 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).

Approximately 55% of patients enrolled in each treatment arm were considered fully evaluable for microbiologic efficacy. The major reason for nonevaluability in each treatment arm was that the patient did not satisfy the baseline criteria for a proven bacteriologic infection. Table 2 below summarizes reasons for patient exclusion from the fully evaluable for microbiologic efficacy analysis set.

Reviewer's Note: Reasons for nonevaluability were generally similar between the treatment arms.

A sizable number of patients were excluded due to negative baseline cultures, causing some concern about whether randomization is preserved in the fully evaluable for microbiologic efficacy analysis set. However, there is nothing in the results to suggest that randomization is compromised in this analysis set (e.g., observed baseline covariates are similar between the treatment groups). In addition, efficacy results in this analysis set are similar to those found in the ITT set which includes patients regardless of baseline culture status.

Table 2. Primary Reasons for Microbiologic Nonevaluability: Intent-to-Treat Population

Reasons	Levofloxacin N=298	FLOXIN N=296
Bacteriologic infection not proven[b]	131	118
Effective concomitant therapy	4	0
Inappropriate bacteriologic culture	4	7
Insufficient course of therapy[c]	1	3
Other protocol violation	1	0
Unevaluable for safety	0	3
Total unevaluable for microbiologic efficacy	141 (47.3)	131 (44.3)

[a] Subjects counted only once.
[b] Of subjects in this category, 55 levofloxacin-treated subjects and 49 FLOXIN-treated subjects are possibly microbiologically evaluable (i.e., pathogen identified in the admission culture at $\geq 10^3$ cfu/mL but $<10^5$ cfu/mL).
[c] Subject 18015 (levofloxacin group) was enrolled inappropriately as she had a complicated UTI.

Demographic and baseline (admission) characteristics were comparable between the levofloxacin and ofloxacin treatment groups for each of the analysis sets. In the intent-to-treat population, the mean age for all subjects was 31.6 years with a range [redacted] years. Women accounted for all subjects enrolled and 77.6% of subjects were Caucasian.

Table 3 summarizes microbiologic eradication rates for all admission pathogens (both definite and possible) for subjects fully evaluable for microbiologic efficacy. Table 4 summarizes microbiologic eradication rates for all definite admission pathogens for subjects fully evaluable for microbiologic efficacy.

Reviewer's Note: Levofloxacin eradication rates were similar to ofloxacin eradication rates in both analyses.

Confidence intervals produced by the sponsor are for the difference in rates, ofloxacin minus levofloxacin. Thus the upper bound is the one of most interest (i.e., the upper bound suggests the extent to which levofloxacin might be inferior to ofloxacin in terms of the response rate). Reviewer confidence intervals will be calculated for the difference, levofloxacin minus ofloxacin.

Table 3. Microbiologic Eradication Rates Based on All Admission Pathogens Summarized by Pathogen Category and Pathogen: Subjects Fully Evaluable for Microbiologic Efficacy

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 4. Microbiologic Eradication Rates Based on Definite (≥10^5 cfu/mL) Admission Pathogens Summarized by Pathogen Category and Pathogen: Subjects Fully Evaluable for Microbiologic Efficacy

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%.

Results were similar for the other analysis sets (Figure 1) and also for various age and race subgroups. Results were also generally consistent across centers.

Reviewer's Note: Results are generally consistent across analysis sets.

As can be seen in Figure 1, levofloxacin eradication rates were least promising as compared to ofloxacin in the possibly microbiologically evaluable set of patients (87% eradication for levofloxacin versus 94% for ofloxacin). These are patients with admission pathogens identified at ≥10^3 cfu/mL but <10^5 cfu/mL. There are relatively few patients included in this analysis set, however, increasing the variability associated with the point estimate of the difference.

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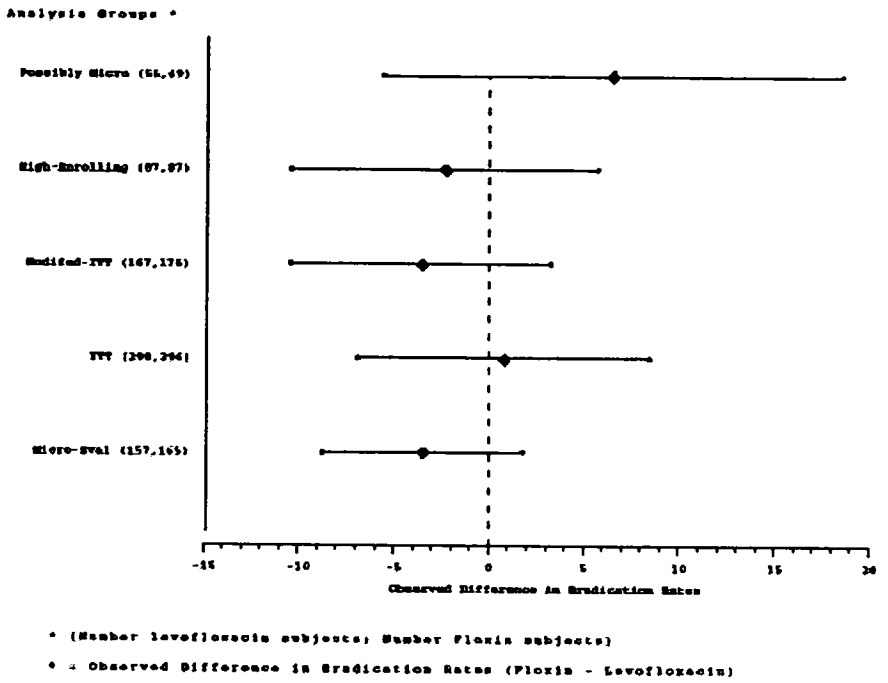
Figure 1. 95% Confidence Intervals for Treatment Differences in Eradication Rates by Analysis Group



Eight (5.1%) of 157 levofloxacin-treated subjects and three (1.8%) of 165 ofloxacin-treated subjects fully evaluable for microbiologic efficacy had a documented microbiologic relapse. Three (1.9%) levofloxacin subjects and eleven (6.7%) ofloxacin subjects were presumed to have microbiologic relapse based on clinical signs and symptoms of UTI necessitating antibiotic therapy but had unknown urine culture results.

Reviewer's Note: *Overall (documented plus presumed) microbiologic relapse rates, as calculated by the sponsor, were similar between levofloxacin and ofloxacin.*

There were 12 (7.6%) levofloxacin and 8 (4.8%) ofloxacin patients with organisms present at baseline, eradicated at posttherapy, and isolated at poststudy at $\geq 10^3$ cfu/mL but $< 10^5$ cfu/mL who were assigned a response of eradicated poststudy by the sponsor. Using the original definition these patients would be assessed as relapses, bringing the documented relapse rate to 12.7% for levofloxacin and 6.7% for ofloxacin (p=0.097 from a chi-squared test of equality). Revised overall (documented plus presumed) relapse rates were again similar for the groups: 14.6% for levofloxacin and 13.3% for ofloxacin.

Among subjects fully evaluable for microbiologic efficacy, clinical cure rates were similar for the two treatment groups (86.6% for levofloxacin, 88.5% for ofloxacin). Clinical success (cure + improvement) rates were also similar, 98.1% for levofloxacin-treated subjects and 97.0% for ofloxacin-treated subjects, with a 95% confidence interval of [-4.8, 2.6] for the difference. Table 5 summarizes clinical response by admission pathogen (both definite and possible) for subjects fully evaluable for microbiologic efficacy. Table 6 summarizes this information for definite admission pathogens only.

Table 5. Clinical Response Based on All Admission Pathogens for Subjects With Pathogens of Primary Interest[a]: Subjects Fully Evaluable for Microbiologic Efficacy

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.

Table 6. Clinical Response Based on Definite (≥10 5 cfu/mL) Admission Pathogens for Subjects With Pathogens of Primary Interest [a]: Subjects Fully Evaluable for Microbiologic Efficacy

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.

Clinical response rates were similar for the other analysis populations. Clinical response rates were also generally consistent across centers and various demographic subgroups (e.g., age and race).

Safety information was unavailable for three subjects (4029, 26018, and 60029) in the ofloxacin group who were lost to follow-up. These subjects are excluded from the safety analysis.

Table 7 summarizes extent of exposure for the intent-to-treat population.

Table 7. Extent of Exposure to Therapy: Intent-to-Treat Population

Extent of Therapy	No. (%) of Subjects: Levofloxacin (N=298)	FLOXIN (N=296)
Days on Therapy[a]		
Unknown	0 (0.0)	3 (1.0)
1	0 (0.0)	2 (0.7)
2	0 (0.0)	2 (0.7)
3	285 (95.6)	281 (94.9)
4	13 (4.4)	8 (2.7)
N	298 (100.0)	293 (99.0)
Mean±SD	3.0± 0.20	3.0± 0.25
Median	3.0	3.0
Range		
Missing	0 (0.0)	3 (1.0)
Number of Doses[b]		
Total with Dosing Information	298 (100.0)	293 (99.0)
Mean±SD	6.0±0.10	5.9±0.43
Median	6.0	6.0
Range		
Total with Unknown Dosing Information	0 (0.0)	3 (1.0)

[a] The total planned duration of therapy for Levofloxacin and FLOXIN was 3 days. Days on therapy was defined as (last day-first day)+1.

[b] Levofloxacin had a q24h dosing schedule and FLOXIN had a q12h dosing schedule. However, Levofloxacin-treated subjects received study drug (Levofloxacin or placebo) q12h to maintain double-blind dosing.

Table 8 summarizes frequently reported adverse events by body system and treatment group.

Table 8. Incidence of Frequently Reported (≥2%)[a] Adverse Events: Summarized by Body System and Primary Term: Subjects Evaluable for Safety

Body System/Primary Term	No. (%) of Subjects	
	Levofloxacin (N=298)	FLOXIN (N=293)
All body systems	90 (30.2)	96 (32.8)
Skin and appendages disorders		
Pruritus genital	5 (1.7)	6 (2.0)
Central & peripheral nervous system disorders		
Headache	15 (5.0)	23 (7.8)
Dizziness	0 (0.0)	6 (2.0)
Psychiatric disorders		
Insomnia[b]	2 (5.7) (N=35)	2 (6.7) (N=30)
Dreaming abnormal[b]	1 (2.9) (N=35)	3 (10.0) (N=30)
Paroniria[b]	0 (0.0) (N=35)	1 (3.3) (N=30)
Gastrointestinal system disorders		
Nausea	11 (3.7)	9 (3.1)
Abdominal pain	9 (3.0)	14 (4.8)
Diarrhea	6 (2.0)	9 (3.1)
Dyspepsia	3 (1.0)	6 (2.0)
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.

Two hundred sixty-three levofloxacin- and 264 ofloxacin-treated subjects volunteered to take part in the interactive voice response (IVR) survey. Subjects who agreed to take part in this survey were told that quinolones could cause sleep disorders, including trouble sleeping and abnormal dreams. One hundred thirteen (43%) levofloxacin-treated subjects and 163 (61.7%) ofloxacin-treated subjects reported either trouble sleeping or unusual dreams or both.

III. CONCLUSIONS

1. Therapeutic equivalence of levofloxacin to ofloxacin was demonstrated for the primary efficacy endpoint, microbiologic response posttherapy in subjects fully evaluable for microbiologic efficacy, using a delta of 10%. The subject eradication rate was 96.2% for levofloxacin and 92.7% for ofloxacin, with a corresponding 95% confidence interval for the difference in rates, levofloxacin minus ofloxacin, of (-3.1%, 10.8%). Results were similar across analysis groups, centers, and certain demographic subgroups (i.e., age and race).

The comparator, 200 mg ofloxacin taken orally twice daily for three days, is not an approved product for this indication. The approved ofloxacin regimen for use in uncomplicated UTI is 200 mg ofloxacin taken orally twice daily for seven days. However, the control regimen used in this trial did appear to be active. In addition, if we assumed that the seven day ofloxacin regimen could obtain a 100% eradication rate in the population studied, levofloxacin would still be able to show therapeutic equivalence to this regimen using a delta of 10%. The 95% confidence interval for the difference between levofloxacin (96.2%) and ofloxacin (100%, under the worst-case [for levofloxacin] assumption that all patients would have been eradicated had they been treated with ofloxacin for 7 days instead of the 3 days given in this study) would be (-9.6%, 0.7%).

2. Adverse event rates appeared similar for levofloxacin and ofloxacin.

RECOMMENDED REGULATORY ACTION:

The data provided by the applicant in this submission support the conclusion that efficacy and safety are similar for 250 mg levofloxacin taken orally once daily for three days and 200 mg ofloxacin taken orally twice daily for three days.

/S/ 12/2/98

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APPEARS THIS WAY
ON ORIGINAL

/S/ 12/2/98

Concur: Mohammad Huque, Ph.D.
Director, DB III

cc:
Orig. NDA #20-634/S-004
Orig. NDA #20-635/S-003
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Dr. Hopkins
HFD-590/Dr. Sacks
HFD-590/Ms. Anderson
HFD-725/Dr. Huque
HFD-725/Dr. Silliman
HFD-725/Ms. Shores
HFD-344/Dr. Thomas
This review contains 13 pages.

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