

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-199

MICROBIOLOGY REVIEW

**REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY OR OFFICE OF GENERIC
DRUGS
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW # 1 OF NDA**

March 22, 2000

- A.
1. NDA/ANDA/IND/: NDA 21-199
 2. TYPE OF SUPPLEMENT: NA
 3. SUPPLEMENT PROVIDES FOR: NA
 4. APPLICANT/SPONSOR: Santen Incorporated
555 Gateway Drive
Napa, California 94558
 5. MANUFACTURING SITE: Napa, California
 6. DRUG PRODUCT NAME:
Proprietary: QUIXIN™
Nonproprietary: Levofloxacin Ophthalmic Solution, 0.5%
Drug Priority Classification: 1
 6. DOSAGE FORM, ROUTE OF ADMINISTRATION AND
STRENGTH/POTENCY: Ophthalmic solution 0.5%, q 2h up to 8x/day on
days 1 and 2, and q 4h up to 4x/day on days 3
through 5.
 8. METHOD (S) OF STERILIZATION:
 9. PHARMACOLOGICAL CATEGORY: Antibiotic solution
- B.
1. DOCUMENT/LETTER DATE: February 28, 2000
 2. RECEIPT DATE: March 01, 2000
 3. CONSULT DATE: March 03, 2000
 4. DATE OF AMENDMENT: NA
 5. ASSIGNED FOR REVIEW: March 07, 2000
 6. SUPPORTING/RELATED DOCUMENTS: None -

C. **REMARKS:** The consult requests review of a New Drug Application for 0.5% Levofloxacin Ophthalmic solution (QUIXIN™) which was licensed from Daiichi Pharmaceuticals, Inc. (NDA 20-634). Daiichi manufactures and markets systemic levofloxacin formulations ex-US for treatment of systemic infections. [redacted]

[redacted] The consult requests a microbiology review of this original NDA 21-199 submitted by Santen Incorporated (Santen Inc., Napa, CA).

D. **CONCLUSIONS:** The Microbiology section of this supplement is recommended for approval based on the information provided.

/S/ 5/17/00

Vinnie Pawar, Ph.D.

cc:

- Original NDA 21-199
- HFD 550/Div. File
- HFD 160/Consult
- HFD 550/Mike Puglisi
- HFD 160/Microbiologist/V.Pawar [HFD-805]

5/17/00

[redacted]

APPROVED THIS WAY
ON ORIGINAL

APR 14 2000

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

Consultative Review for HFD-550
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products

Requestor: Mike Puglisi, CSO HFD-550

Date of Request: March 15, 2000

Reason for Request: Microbiological Review for efficacy and safety

NDA #: 21-199

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	28-FEB-00
CDER DATE:	01-MAR-00
REVIEW ASSIGN DATE:	15-MAR-00
REVIEW COMPLETE DATE:	06-APR-00

SPONSOR: Santen Incorporated
555 Gateway Drive
Napa, California 94558

CONTACT PERSON: Michelle Carpenter
Director, Regulatory Affairs
Phone Number: (707) 256-2453

SUBMISSION REVIEWED: Original NDA submission

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Bacterial Conjunctivitis

DOSAGE FORM: Sterile ophthalmic solution

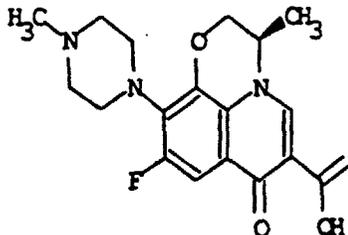
DRUG PRODUCT NAME

<u>PROPRIETARY:</u>	QUIXIN™
<u>NONPROPRIETARY/USAN:</u>	Levofloxacin ophthalmic solution
<u>CHEMICAL NAME:</u>	(-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyloxy)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid hemihydrate.

NDA #21-199
Santen Incorporated
0.5% Levofloxacin Ophthalmic Solution

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STRUCTURAL FORMULA:



• 1/2 H₂O

Molecular Formula: C₁₈H₂₀FN₃O₄ • 1/2 H₂O
Molecular Weight: 370.38

SUPPORTING DOCUMENTS:

[redacted] —Santen Levofloxacin ophthalmic solution
NDA 20-634—RW Johnson Levofloxacin Tablets
NDA 20-635—RW Johnson Levofloxacin Injection
[redacted] Daiichi Pharmaceutical Co, Ltd. —levofloxacin drug substance

REMARKS/COMMENTS:

This application is for a 0.5% levofloxacin ophthalmic solution. The proposed indication for the product is the treatment of bacterial conjunctivitis, in both adults and children 1 year of age or older. The proposed dosing regimen is every 2 hours up to 8 times a day on days 1 and 2, and every 4 hours up to 4 times a day on days 3 through 5.

Two pivotal studies have been performed to support this indication. Study 03-003 evaluated the safety and efficacy of 0.5 % levofloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution in 200 patients. Study 03-004 evaluated the safety and efficacy of 0.5% levofloxacin ophthalmic solution versus placebo in 100 patients.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when the recommended changes are made to the MICROBIOLOGY subsection of the package insert. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 40-45.

Microbiological Review

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EXECUTIVE SUMMARY

Bacterial conjunctivitis is a common eye disease encountered by the ophthalmologist. The treatment regimen usually involves the use of an antimicrobial agent to control or manage the disease. Antimicrobial therapy usually proves beneficial by removing the etiological agents and reducing the ocular signs of the disease. The most frequent bacterial causes include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

Data from the original levofloxacin NDA which was collected in the early 1990's produced the MICs summarized in TABLE A. The susceptible breakpoint in systemic infections is ≤ 2.0 $\mu\text{g/mL}$.

In vitro Activity of Levofloxacin in Original NDA 20-634

Species	No. of Isolates	Median MIC ₉₀ ($\mu\text{g/mL}$)
<i>Enterococcus faecalis</i>	1540	1.56
<i>Streptococcus pyogenes</i>	660	1.56
<i>Staphylococcus aureus</i> (MS)	1272	0.50
<i>Staphylococcus aureus</i> (MR)	1722	0.78
<i>Staphylococcus epidermidis</i>	582	0.78
<i>Streptococcus pneumoniae</i>	941	1.56
<i>Acinetobacter baumannii</i>	100	2.25
<i>Acinetobacter calcoaceticus</i>	230	0.39
<i>Acinetobacter lwoffii</i>	31	0.25
<i>Enterobacter cloacae</i>	1480	0.39
<i>Escherichia coli</i>	5647	0.10
<i>Haemophilus influenzae</i>	1013	0.03
<i>Klebsiella pneumoniae</i>	2369	0.25
<i>Morganella morganii</i>	699	0.13
<i>Neisseria gonorrhoeae</i>	464	0.03
<i>Proteus mirabilis</i>	1058	0.19
<i>Pseudomonas aeruginosa</i>	3558	3.13
<i>Serratia marcescens</i>	1292	3.13
<i>Bacteroides fragilis</i>	581	4.00

A literature search submitted with a recent supplement to the original NDA suggest that the median MIC₉₀ value has increased for several of these pathogens. As expected the values have increased dramatically against *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*. These two species have been the ones that have the greatest quinolone resistance problem. The median MIC₉₀ value has increased to 16 $\mu\text{g/mL}$ for both of these species. *Enterococcus faecalis* has also shown an increase in the median MIC₉₀ value to >4 $\mu\text{g/mL}$.

In the Phase III clinical studies conjunctiva swab specimens from patients were sent to an independent laboratory for bacterial culture and identification of genus and species of the potential pathogens. The *in vitro* susceptibilities of ocular isolates to levofloxacin were determined by both [redacted] and [redacted] methods according to NCCLS recommendations.

A total of 884 bacterial isolates, representing 70 distinct species, were obtained from 359 patients. To avoid sample bias in favor of the most common organisms, no more than 20 strains of any one species were tested. For disk diffusion testing, all species having ≤ 20 isolates were evaluated, while those with more than 20 isolates had 20 selected for evaluation using a computer generated randomization scheme. The criteria for [redacted] testing was identical to [redacted] except that only the most common ocular pathogens were tested. NCCLS testing methods were used.

The following interpretative criteria were used:

	Drug	Disk Diffusion (mm)			Broth Dilution ($\mu\text{g}/\text{mL}$)		
		S	I	R	S	I	R
Organisms other than <i>Haemophilus</i> species	LVFX	≥ 17	14-16	≤ 13	≤ 2	4	≥ 8
	CPLX	≥ 21	16-20	≤ 15	≤ 1	2	≥ 4
	OFLX	≥ 16	13-15	≤ 12	≤ 2	4	≥ 8
For <i>Haemophilus</i> species	LVFX	≥ 17	N/A	≤ 16	≤ 2	N/A	≥ 4
	CPLX	≥ 21	N/A	≤ 20	≤ 1	N/A	≥ 2
	OFLX	≥ 16	N/A	≤ 15	≤ 2	N/A	≥ 4

Abbreviations: S-Susceptible, I-Intermediate, R-Resistant

LVFX-levofloxacin, CPLX-ciprofloxacin, OFLX-ofloxacin

These are NCCLS criteria, except NCCLS has only a susceptible category for *Haemophilus* species.

A total of 232 (103 gram-negative and 129 gram-positive) of the clinical isolates were tested for susceptibility. Of the 103 gram-negative organisms, 101 were tested by [redacted] and 73 were tested by [redacted]. Of the 129 gram-positive isolates tested by [redacted] 113 were also tested by [redacted]. Only four *Pseudomonas* species were tested by [redacted] and the levofloxacin MIC₉₀ value was 0.5 $\mu\text{g}/\text{mL}$. The ciprofloxacin MIC₉₀ value for these *Pseudomonas* species was only 0.12 $\mu\text{g}/\text{mL}$. The MIC₉₀ value for forth-eight tested *Staphylococcus* species was 0.25 $\mu\text{g}/\text{mL}$. The ciprofloxacin MIC₉₀ value was higher at 0.5 $\mu\text{g}/\text{mL}$. Only one gram-negative isolate was levofloxacin resistant. This was a *Brevundimonas vesicularis* isolate. The levofloxacin and ciprofloxacin MIC value for this organism was 8.0 $\mu\text{g}/\text{mL}$. As expected the ofloxacin MIC value of 16 $\mu\text{g}/\text{mL}$ was double the levofloxacin value. Two *Staphylococcus epidermidis* isolates were levofloxacin resistant by [redacted] (one of the two was intermediate by [redacted]). One of these two isolates had MICs of 16 $\mu\text{g}/\text{mL}$, >16 $\mu\text{g}/\text{mL}$, and 32 $\mu\text{g}/\text{mL}$ for levofloxacin, ciprofloxacin, and ofloxacin, respectively. The other isolates had MICs of 4 $\mu\text{g}/\text{mL}$, 4 $\mu\text{g}/\text{mL}$, 8 $\mu\text{g}/\text{mL}$, for levofloxacin, ciprofloxacin, and ofloxacin, respectively. TABLE B shows a summary of the microbial eradication rates by organism in the two studies. No susceptibility testing was performed on isolates after treatment, therefore, no conclusions can be made on whether treatment leads to organisms with increased MIC values.

TABLE B
 Microbial Eradication Rate by Organism in Phase III Trials

Organism	Treatment		
	0.5% LVFX n ¹ (%)	0.3 % OFLX n (%)	Placebo n (%)
Gram-negative isolates			
Enterobacter/Pantoea	1/1 (100.0)		1/1 (100.0)
<i>Escherichia coli</i>	1/1 (100.0)		
<i>Proteus mirabilis</i>	3/3 (100.0)		1/1 (100.0)
<i>Serratia marcescens</i>	4/4 (100.0)	1/1 (100.0)	1/1 (100.0)
Haemophilus	52/56 (92.9)	33/37 (89.2)	12/23 (52.2)
<i>H. influenzae</i>	40/53 (92.5)	32/36 (88.9)	12/23 (52.2)
<i>H. parainfluenzae</i>	3/3 (100.0)	1/1 (100.0)	
Other Neisseria	1/1 (100.0)	1/1 (100.0)	
Moraxella	1/1 (100.0)		1/1 (100.0)
Acinetobacter	6/7 (85.7)	3/4 (75.0)	3/3 (100.0)
Pseudomonas	6/6 (100.0)	2/3 (66.7)	
<i>P. aeruginosa</i>		0/1 (0.0)	
Other Ps./Other Non-Enterobacteriaceae	6/6 (100.0)	2/2 (100.0)	
Total Gram-negative isolates	75/80 (93.3)	40/46 (87.0)	19/30 (63.3)
Gram-Positive isolates			
Corynebacterium	5/5 (100.0)	2/2 (100.0)	
Staphylococcus	49/49 (100.0)	36/36 (100.0)	14/15 (93.3)
<i>S. aureus</i>	24/24 (100.0)	19/19 (100.0)	5/6 (83.3)
<i>S. epidermidis</i>	22/22 (100.0)	15/15 (100.0)	7/7 (100.0)
Other coagulase negative	3/3 (100.0)	2/2 (100.0)	2/2 (100.0)
Micrococcus/Stomatococcus	4/4 (100.0)	1/1 (100.0)	1/1 (100.0)
Streptococcus	61/69 (88.4)	22/30 (73.3)	13/23 (56.5)
Streptococcus, Group β-hemolytic (<i>S. pyogenes</i>)	1/1 (100.0)		
<i>S. pneumoniae</i>	45/53 (84.9)	17/25 (68.0)	9/19 (47.4)
Streptococcus (Groups D, G-Nongrouped; viridans)	15/15 (100.0)	5/5 (100.0)	4/4 (100.0)
Total Gram-positive isolates	119/127 (93.7)	61/69 (88.4)	28/39 (71.8)
Total isolates	194/207 (93.7)	101/115 (87.8)	47/69 (68.1)

¹ Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline

It appears that eradication rates were slightly better in the levofloxacin group than in the ofloxacin group. This is what is expected since levofloxacin is the L-isomer of ofloxacin and almost all of ofloxacin's activity resides in the L-isomer. Levofloxacin appears to do better

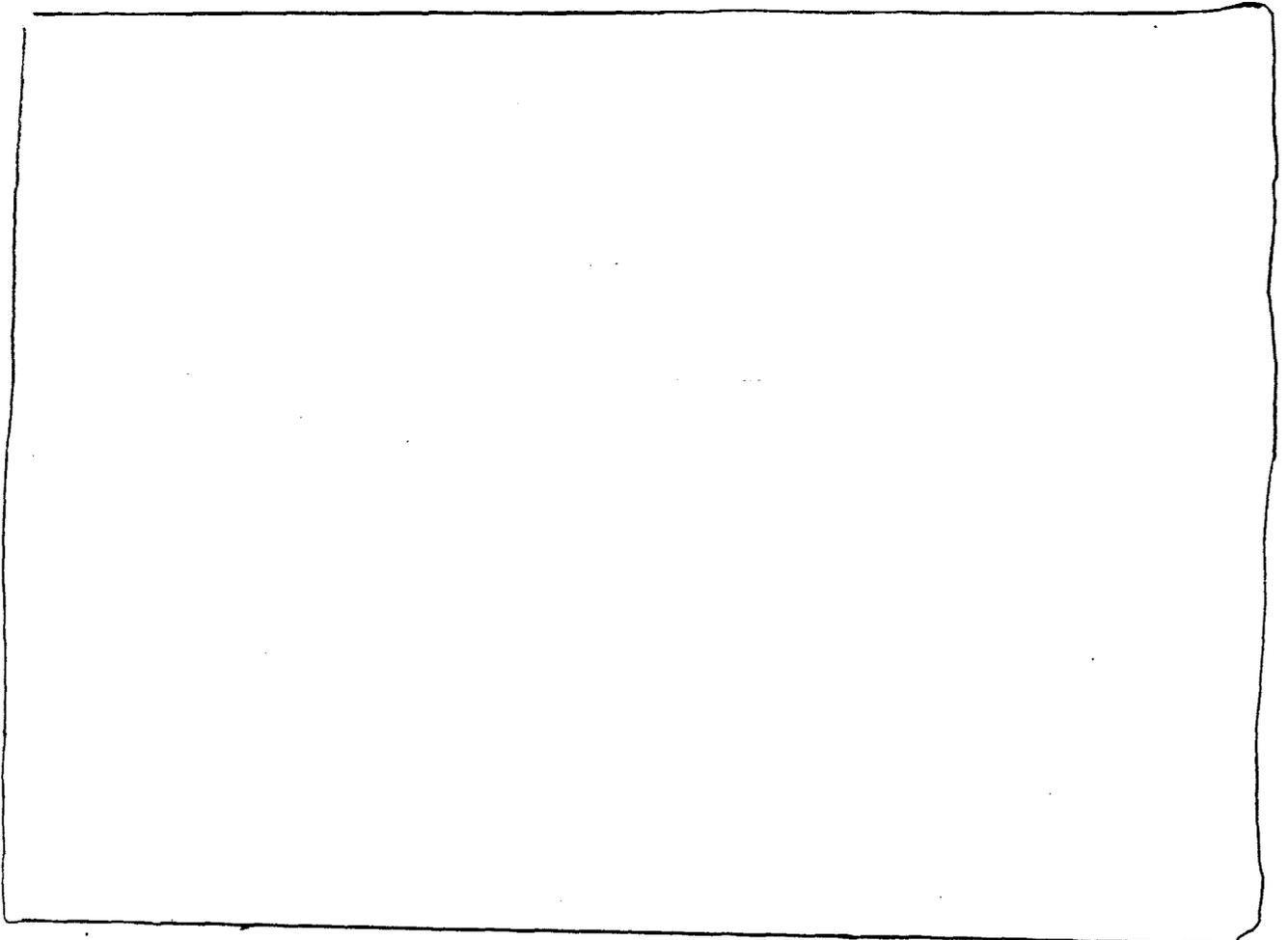
against the streptococci. Most streptococci are close to the susceptible breakpoint for these drugs and since levofloxacin is about twice as active as ofloxacin it should produce better results.

Three animal model studies of ocular disease were performed to evaluate the efficacy of levofloxacin against two of the most common organisms causing ocular infections. Levofloxacin was effective in all three studies. Another study with a different formulation showed levofloxacin was effective against *P. aeruginosa* caused keratitis in rabbits.

Studies show that after ocular administration levofloxacin blood levels are low (2.15 ng/mL). Mean levofloxacin concentrations in tears after administration of one drop in each eye ranged from 34.9 to 221.1 $\mu\text{g/mL}$ during the first 60 minute period and the mean tear concentration measured 4 hours after a single ophthalmic dose was 17.04 $\mu\text{g/mL}$. The lower limit of the 95% confidence interval was 10.0 $\mu\text{g/mL}$ for the 2 hr postdose testing period and 1.9 $\mu\text{g/mL}$ at 4 hours. These concentrations are above the systemic susceptible breakpoint of 2 $\mu\text{g/mL}$ for most of the time period between doses.

PRECLINICAL EFFICACY

MODE OF ACTION



2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Levofloxacin has been shown to have activity against a wide variety of gram-positive and gram-negative bacteria. TABLE 1 is a tabular presentation of data contrasting the *in vitro* antimicrobial activity of levofloxacin with other fluoroquinolones in ophthalmic clinical use in the United States. This presentation includes data from the original levofloxacin NDA (RW Johnson) for levofloxacin tablets and data from Santen Study PC003-01R, which used ocular isolates collected from bacterial conjunctivitis patients in the pivotal Phase III trials.

TABLE 1
In Vitro Comparison of Fluoroquinolones in Ophthalmic Use

Organism	Drug	RW Johnson		Santen	
		No. of Isolates Tested	Median MIC ₉₀ (µg/mL)	No. of Isolates Tested	Median MIC ₉₀ (µg/mL)
Gram-Positive (Aerobes)					
<i>Bacillus</i> species	Levofloxacin	N/A	—	1	0.12
	Ofloxacin	N/A	—	1	0.25
	Ciprofloxacin	N/A	—	1	0.06
	Norfloxacin	N/A	—	N/A	—
<i>Enterococcus faecalis</i>	Levofloxacin	1540	1.56	2	1.00
	Ofloxacin	1441	4.00	2	2.00
	Ciprofloxacin	1431	1.56	2	1.00
	Norfloxacin	610	6.25	N/A	—
<i>Staphylococcus aureus</i>	Levofloxacin	3396	0.39	18	0.25
	Ofloxacin	3285	0.78	18	0.50
	Ciprofloxacin	3025	1.00	18	0.50
	Norfloxacin	812	25.00	N/A	—
<i>Staphylococcus capitis</i>	Levofloxacin	N/A	—	1	0.25
	Ofloxacin	N/A	—	1	0.50
	Ciprofloxacin	N/A	—	1	0.12
	Norfloxacin	N/A	—	N/A	—
<i>Staphylococcus epidermidis</i>	Levofloxacin	582	0.78	20	0.25
	Ofloxacin	659	1.56	20	0.50
	Ciprofloxacin	671	1.17	20	1.00
	Norfloxacin	138	0.50	N/A	—
<i>Staphylococcus haemolyticus</i>	Levofloxacin	N/A	—	5	0.25
	Ofloxacin	N/A	—	5	0.50
	Ciprofloxacin	N/A	—	5	0.25
	Norfloxacin	N/A	—	N/A	—
<i>Staphylococcus hominis</i>	Levofloxacin	N/A	—	3	0.12
	Ofloxacin	N/A	—	3	0.25
	Ciprofloxacin	N/A	—	3	0.12
	Norfloxacin	N/A	—	N/A	—
<i>Staphylococcus simulans</i>	Levofloxacin	N/A	—	1	0.25
	Ofloxacin	N/A	—	1	0.50
	Ciprofloxacin	N/A	—	1	0.25
	Norfloxacin	N/A	—	N/A	—

N/A = not available, testing not conducted

TABLE 1 (continued)
 In Vitro Comparison of Fluoroquinolones in Ophthalmic Use

Organism	Drug	RW Johnson		Santen	
		No. of Isolates Tested	Median MIC ₉₀ (µg/mL)	No. of Isolates Tested	Median MIC ₉₀ (µg/mL)
Gram-Positive (Aerobes) (Cont)					
<i>Stomatococcus mucilaginosus</i>	Levofloxacin	N/A	—	2	0.25
	Ofloxacin	N/A	—	2	0.50
	Ciprofloxacin	N/A	—	2	0.50
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus adjacens</i>	Levofloxacin	N/A	—	1	1.00
	Ofloxacin	N/A	—	1	2.00
	Ciprofloxacin	N/A	—	1	2.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus agalactiae</i>	Levofloxacin	N/A	—	1	1.00
	Ofloxacin	N/A	—	1	2.00
	Ciprofloxacin	N/A	—	1	1.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus bovis</i>	Levofloxacin	N/A	—	1	1.00
	Ofloxacin	N/A	—	1	2.00
	Ciprofloxacin	N/A	—	1	2.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus constellatus</i>	Levofloxacin	N/A	—	1	1.00
	Ofloxacin	N/A	—	1	2.00
	Ciprofloxacin	N/A	—	1	2.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus gordonii</i>	Levofloxacin	N/A	—	2	0.50
	Ofloxacin	N/A	—	2	1.00
	Ciprofloxacin	N/A	—	2	0.50
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus intermedius</i>	Levofloxacin	N/A	—	3	2.00
	Ofloxacin	N/A	—	3	4.00
	Ciprofloxacin	N/A	—	3	8.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus salivarius</i>	Levofloxacin	N/A	—	5	1.00
	Ofloxacin	N/A	—	5	2.00
	Ciprofloxacin	N/A	—	5	1.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus mitis</i>	Levofloxacin	N/A	—	14	2.00
	Ofloxacin	N/A	—	14	4.00
	Ciprofloxacin	N/A	—	14	4.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus oralis</i>	Levofloxacin	N/A	—	11	2.00
	Ofloxacin	N/A	—	11	2.00
	Ciprofloxacin	N/A	—	11	4.00
	Norfloxacin	N/A	—	N/A	—
<i>Streptococcus pneumoniae</i>	Levofloxacin	941	1.56	19	1.00
	Ofloxacin	762	3.13	19	2.00
	Ciprofloxacin	857	1.56	19	1.00
	Norfloxacin	136	12.50	N/A	—

N/A = not available, testing not conducted

TABLE 1 (continued)
 In Vitro Comparison of Fluoroquinolones in Ophthalmic Use

Organism	Drug	RW Johnson		Santen	
		No. of Isolates Tested	Median MIC ₉₀ (µg/mL)	No. of Isolates Tested	Median MIC ₉₀ (µg/mL)
Gram-Positive (Aerobes) (Cont)					
<i>Streptococcus pyogenes</i>	Levofloxacin	660	1.56	1	0.50
	Ofloxacin	585	1.56	1	1.00
	Ciprofloxacin	466	1.56	1	0.25
	Norfloxacin	127	12.50	N/A	—
Gram-Negative (Aerobes)					
<i>Acinetobacter baumannii</i>	Levofloxacin	100	2.25	N/A	—
	Ofloxacin	100	2.25	N/A	—
	Ciprofloxacin	100	1.25	N/A	—
	Norfloxacin	90	8.00	N/A	—
<i>Acinetobacter calcoaceticus</i>	Levofloxacin	230	0.39	N/A	—
	Ofloxacin	220	0.78	N/A	—
	Ciprofloxacin	220	0.78	N/A	—
	Norfloxacin	27	25.00	N/A	—
<i>Acinetobacter lwoffii</i>	Levofloxacin	31	0.25	N/A	—
	Ofloxacin	31	0.5	N/A	—
	Ciprofloxacin	31	0.19	N/A	—
	Norfloxacin	N/A	—	N/A	—
<i>Aeromonas caviae</i>	Levofloxacin	N/A	—	1	0.015
	Ofloxacin	N/A	—	1	≤ 0.03
	Ciprofloxacin	N/A	—	1	≤ 0.008
	Norfloxacin	N/A	—	N/A	—
<i>Aeromonas hydrophila</i>	Levofloxacin	10	0.25	1	0.03
	Ofloxacin	10	0.5	1	0.06
	Ciprofloxacin	10	0.25	1	0.015
	Norfloxacin	N/A	—	N/A	—
<i>Brevundimonas vesicularis</i>	Levofloxacin	N/A	—	1	8.00
	Ofloxacin	N/A	—	1	16.00
	Ciprofloxacin	N/A	—	1	8.00
	Norfloxacin	N/A	—	N/A	—
<i>Chryseomonas luteola</i>	Levofloxacin	N/A	—	1	0.06
	Ofloxacin	N/A	—	1	0.12
	Ciprofloxacin	N/A	—	1	0.015
	Norfloxacin	N/A	—	N/A	—
<i>Citrobacter freundii</i>	Levofloxacin	N/A	—	1	0.06
	Ofloxacin	N/A	—	1	0.06
	Ciprofloxacin	N/A	—	1	0.12
	Norfloxacin	N/A	—	N/A	—
<i>Enterobacter aerogenes</i>	Levofloxacin	N/A	—	1	0.06
	Ofloxacin	N/A	—	1	0.12
	Ciprofloxacin	N/A	—	1	0.03
	Norfloxacin	N/A	—	N/A	—
<i>Enterobacter agglomerans</i>	Levofloxacin	N/A	—	1	0.06
	Ofloxacin	N/A	—	1	0.12
	Ciprofloxacin	N/A	—	1	0.015
	Norfloxacin	N/A	—	N/A	—

TABLE 1 (Continued)
In Vitro Comparison of Fluoroquinolones in Ophthalmic Use

Organism	Drug	RW Johnson		Santen	
		No. of Isolates Tested	Median MIC ₉₀ (µg/mL)	No. of Isolates Tested	Median MIC ₉₀ (µg/mL)
Gram-Negative (Aerobes) (Cont)					
<i>Enterobacter cloacae</i>	Levofloxacin	1480	0.39	2	0.06
	Ofloxacin	1413	0.78	2	0.12
	Ciprofloxacin	1435	0.20	2	0.03
	Norfloxacin	628	0.39	N/A	—
<i>Escherichia coli</i>	Levofloxacin	5647	0.10	1	0.06
	Ofloxacin	5417	0.19	1	0.06
	Ciprofloxacin	5257	0.05	1	0.015
	Norfloxacin	925	0.12	N/A	—
<i>Flavimonas oryzihabitans</i>	Levofloxacin	N/A	—	1	0.12
	Ofloxacin	N/A	—	1	0.25
	Ciprofloxacin	N/A	—	1	0.06
	Norfloxacin	N/A	—	N/A	—
<i>Haemophilus influenzae</i>	Levofloxacin	1013	0.03	20	0.03
	Ofloxacin	743	0.05	20	0.06
	Ciprofloxacin	797	0.03	20	0.015
	Norfloxacin	409	0.10	N/A	—
<i>Haemophilus parainfluenzae</i>	Levofloxacin	N/A	—	5	0.06
	Ofloxacin	N/A	—	5	0.12
	Ciprofloxacin	N/A	—	5	0.03
	Norfloxacin	N/A	—	N/A	—
<i>Klebsiella oxytoca</i>	Levofloxacin	N/A	—	2	0.03
	Ofloxacin	N/A	—	2	0.06
	Ciprofloxacin	N/A	—	2	≤ 0.008
	Norfloxacin	N/A	—	N/A	—
<i>Klebsiella pneumoniae</i>	Levofloxacin	2369	0.25	3	2.00
	Ofloxacin	2267	0.25	3	4.00
	Ciprofloxacin	2250	0.12	3	8.00
	Norfloxacin	697	0.52	N/A	—
<i>Moraxella oxloensis</i>	Levofloxacin	N/A	—	1	0.03
	Ofloxacin	N/A	—	1	0.06
	Ciprofloxacin	N/A	—	1	≤ 0.008
	Norfloxacin	N/A	—	N/A	—
<i>Morganella morganii</i>	Levofloxacin	699	0.13	N/A	—
	Ofloxacin	672	0.45	N/A	—
	Ciprofloxacin	649	0.10	N/A	—
	Norfloxacin	329	0.39	N/A	—
<i>Neisseria gonorrhoeae</i>	Levofloxacin	464	0.03	N/A	—
	Ofloxacin	235	0.06	N/A	—
	Ciprofloxacin	265	0.01	N/A	—
	Norfloxacin	38	0.06	N/A	—
<i>Neisseria mucosa</i>	Levofloxacin	N/A	—	1	0.03
	Ofloxacin	N/A	—	1	0.06
	Ciprofloxacin	N/A	—	1	≤ 0.008
	Norfloxacin	N/A	—	N/A	—

N/A = not available, testing not conducted

TABLE 1 (Continued)
 In Vitro Comparison of Fluoroquinolones in Ophthalmic Use

Organism	Drug	RW Johnson		Santen	
		No. of Isolates Tested	Median MIC ₉₀ (µg/mL)	No. of Isolates Tested	Median MIC ₉₀ (µg/mL)
Gram-Negative (Aerobes) (Cont)					
<i>Neisseria sicca</i>	Levofloxacin	N/A	—	2	0.03
	Ofloxacin	N/A	—	2	0.06
	Ciprofloxacin	N/A	—	2	≤0.008
	Norfloxacin	N/A	—	N/A	—
<i>Neisseria subflava</i>	Levofloxacin	N/A	—	1	0.03
	Ofloxacin	N/A	—	1	0.06
	Ciprofloxacin	N/A	—	1	≤0.008
	Norfloxacin	N/A	—	N/A	—
<i>Ochrobactrum anthropi</i>	Levofloxacin	N/A	—	1	0.50
	Ofloxacin	N/A	—	1	0.50
	Ciprofloxacin	N/A	—	1	0.25
	Norfloxacin	N/A	—	N/A	—
<i>Pantoea agglomerans</i>	Levofloxacin	N/A	—	1	0.03
	Ofloxacin	N/A	—	1	0.06
	Ciprofloxacin	N/A	—	1	0.015
	Norfloxacin	N/A	—	N/A	—
<i>Proteus mirabilis</i>	Levofloxacin	1058	0.19	5	0.06
	Ofloxacin	1047	0.39	5	0.12
	Ciprofloxacin	918	0.06	5	0.03
	Norfloxacin	415	0.20	N/A	—
<i>Pseudomonas aeruginosa</i>	Levofloxacin	3558	3.13	3	0.50
	Ofloxacin	3367	6.25	3	1.00
	Ciprofloxacin	3230	1.00	3	0.12
	Norfloxacin	715	10.25	N/A	—
<i>Pseudomonas cepacia</i>	Levofloxacin	N/A	—	1	0.03
	Ofloxacin	N/A	—	1	0.12
	Ciprofloxacin	N/A	—	1	0.015
	Norfloxacin	N/A	—	N/A	—
<i>Pseudomonas fluorescens</i>	Levofloxacin	15	2.00	N/A	—
	Ofloxacin	10	4.00	N/A	—
	Ciprofloxacin	10	0.5	N/A	—
	Norfloxacin	N/A	—	N/A	—
<i>Pseudomonas putida</i>	Levofloxacin	17	4.00	N/A	—
	Ofloxacin	12	8.00	N/A	—
	Ciprofloxacin	12	0.5	N/A	—
	Norfloxacin	N/A	—	N/A	—
<i>Serratia marcescens</i>	Levofloxacin	1292	3.13	6	0.25
	Ofloxacin	1243	6.25	6	0.50
	Ciprofloxacin	1189	3.13	6	0.12
	Norfloxacin	635	25.00	N/A	—
<i>Sphingomonas pacimobilis</i>	Levofloxacin	N/A	—	2	0.12
	Ofloxacin	N/A	—	2	0.25
	Ciprofloxacin	N/A	—	2	0.25
	Norfloxacin	N/A	—	N/A	—

N/A = not available, testing not conducted

TABLE 1 (Continued)
 In Vitro Comparison of Fluoroquinolones in Ophthalmic Use

Organism	Drug	RW Johnson		Santen	
		No. of Isolates Tested	Median MIC ₉₀ (µg/mL)	No. of Isolates Tested	Median MIC ₉₀ (µg/mL)
Gram-Negative (Aerobes) (Cont)					
<i>Stenotrophomonas maltophilia</i>	Levofloxacin	N/A	—	3	2.00
	Ofloxacin	N/A	—	3	4.00
	Ciprofloxacin	N/A	—	3	4.00
	Norfloxacin	N/A	—	N/A	—
Gram-Positive (Anaerobes)					
<i>Clostridium perfringens</i>	Levofloxacin	89	0.78	N/A	—
	Ofloxacin	71	1.56	N/A	—
	Ciprofloxacin	40	0.78	N/A	—
	Norfloxacin	32	8.78	N/A	—
<i>Propionibacterium acnes</i>	Levofloxacin	22	0.75	N/A	—
	Ofloxacin	22	1.50	N/A	—
	Ciprofloxacin	3	1.00	N/A	—
	Norfloxacin	2	N/A	N/A	—
Gram-Negative (Anaerobes)					
<i>Bacteroides fragilis</i>	Levofloxacin	581	4.00	N/A	—
	Ofloxacin	499	8.00	N/A	—
	Ciprofloxacin	398	25.00	N/A	—
	Norfloxacin	197	82.00	N/A	—

N/A = not available, testing not conducted

Santen has also submitted a report on the antimicrobial activity of levofloxacin for clinically isolated bacteria identified in patients enrolled in a series of clinical studies of levofloxacin ophthalmic solution and ointment in Japan. In this report the activity of levofloxacin is compared to that of ofloxacin (OFLX), micronomicin (MCR), and cefmenoxime (CMX) against bacterial isolated from patients enrolled in four clinical trials conducted from December, 1995 through August 1996 in Japan. TABLE 2 shows the data for the four studies combined. Only the data for levofloxacin (LVFX) and ofloxacin (OFLX) and species with more than 10 isolates tested are shown. A total of 2211 isolates from 98 species were tested.

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TABLE 2
 Activity against Clinical Isolates in Japanese Studies

Organism	Drug	No. Tested	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<i>Enterococcus faecalis</i>	LVFX	23		2.0	32.0
	OFLX	23		4.0	32.0
<i>Micrococcus species</i>	LVFX	23		1.0	4.0
	OFLX	23		2.0	4.0
<i>Staphylococcus aureus</i>	LVFX	151		0.5	1.0
	OFLX	151		1.0	1.0
<i>Staphylococcus aureus</i> (methicillin-resistant)	LVFX	40		16.0	128.0
	OFLX	40		32.0	>128
<i>Staphylococcus capitis</i>	LVFX	20		0.5	4.0
	OFLX	20		1.0	8.0
<i>Staphylococcus epidermidis</i>	LVFX	473		0.5	16.0
	OFLX	473		1.0	32.0
<i>Staphylococcus haemolyticus</i>	LVFX	12		8.0	32.0
	OFLX	12		8.0	32.0
<i>Staphylococcus hominis</i>	LVFX	22		0.5	4.0
	OFLX	22		0.5	8.0
<i>Streptococcus mitis</i>	LVFX	24		2.0	4.0
	OFLX	24		4.0	8.0
<i>Streptococcus oralis</i>	LVFX	64		2.0	4.0
	OFLX	64		4.0	4.0
<i>Streptococcus pneumoniae</i>	LVFX	39		1.0	2.0
	OFLX	39		2.0	4.0
<i>Bacillus species</i>	LVFX	58		0.25	1.0
	OFLX	58		0.5	2.0
<i>Corynebacterium species</i>	LVFX	190		1.0	4.0
	OFLX	190		1.0	8.0
<i>Moraxella catarrhalis</i>	LVFX	14		≤0.06	0.5
	OFLX	14		0.13	1.0
<i>Acinetobacter baumannii</i>	LVFX	24	0.5	1.0	
	OFLX	24	1.0	1.0	
<i>Acinetobacter species</i>	LVFX	12	0.25	0.5	
	OFLX	12	0.5	1.0	
<i>Agrobacterium radiobacter</i>	LVFX	10	0.13	0.5	
	OFLX	10	0.13	1.0	
<i>Comamonas acidovorans</i>	LVFX	21	-0.5	2.0	
	OFLX	21	1.0	2.0	
<i>Pantoea agglomerans</i>	LVFX	10	0.13	0.25	
	OFLX	10	0.13	0.5	

TABLE 2 (Continued)
 Activity against Clinical Isolates in Japanese Studies

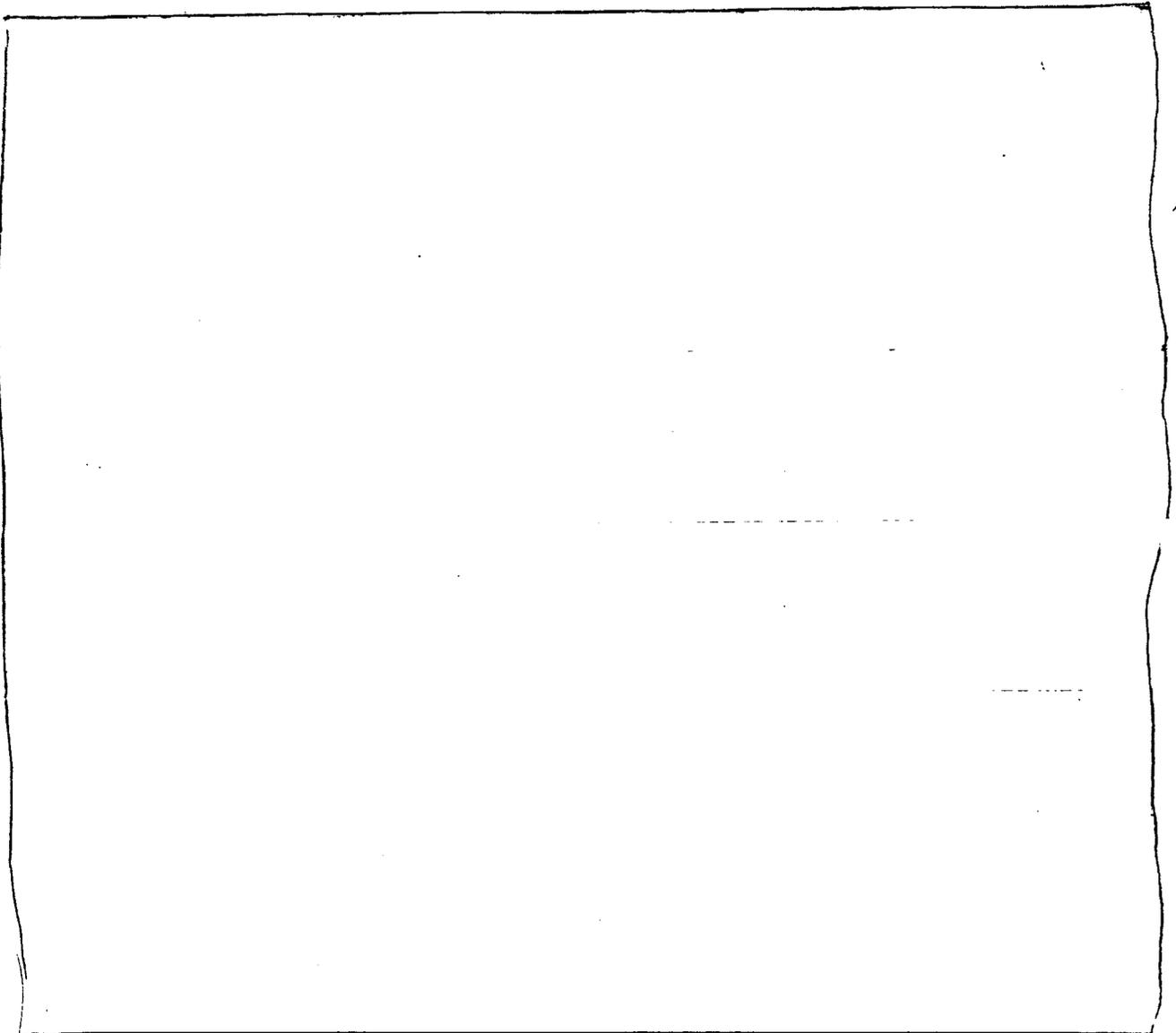
Organism	Drug	No. Tested	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<i>Flavobacterium indologenes</i>	LVFX	13		1.0	8.0
	OFLX	13		2.0	8.0
<i>Haemophilus influenzae</i>	LVFX	23		≤ 0.06	≤ 0.06
	OFLX	23		≤ 0.06	≤ 0.06
<i>Moraxella osloensis</i>	LVFX	28		0.25	0.5
	OFLX	28		0.25	1.0
<i>Pseudomonas aeruginosa</i>	LVFX	31		1.0	4.0
	OFLX	31		2.0	8.0
<i>Burkholderia cepacia</i>	LVFX	12		16.0	64.0
	OFLX	12		16.0	128
<i>Pseudomonas putida</i>	LVFX	15		1.0	4.0
	OFLX	15		2.0	8.0
<i>Brevundimonas vesicularis</i>	LVFX	17		8.0	32.0
	OFLX	17		8.0	64.0
<i>Serratia marcescens</i>	LVFX	14		0.25	1.0
	OFLX	14		0.5	2.0
<i>Sphingomonas paucimobilis</i>	LVFX	14		2.0	8.0
	OFLX	14		2.0	16.0
<i>Stenotrophomonas maltophilia</i>	LVFX	32		4.0	8.0
	OFLX	32		4.0	16.0
<i>Propionibacterium acnes</i>	LVFX	504	0.5	1.0	
	OFLX	504	1.0	1.0	

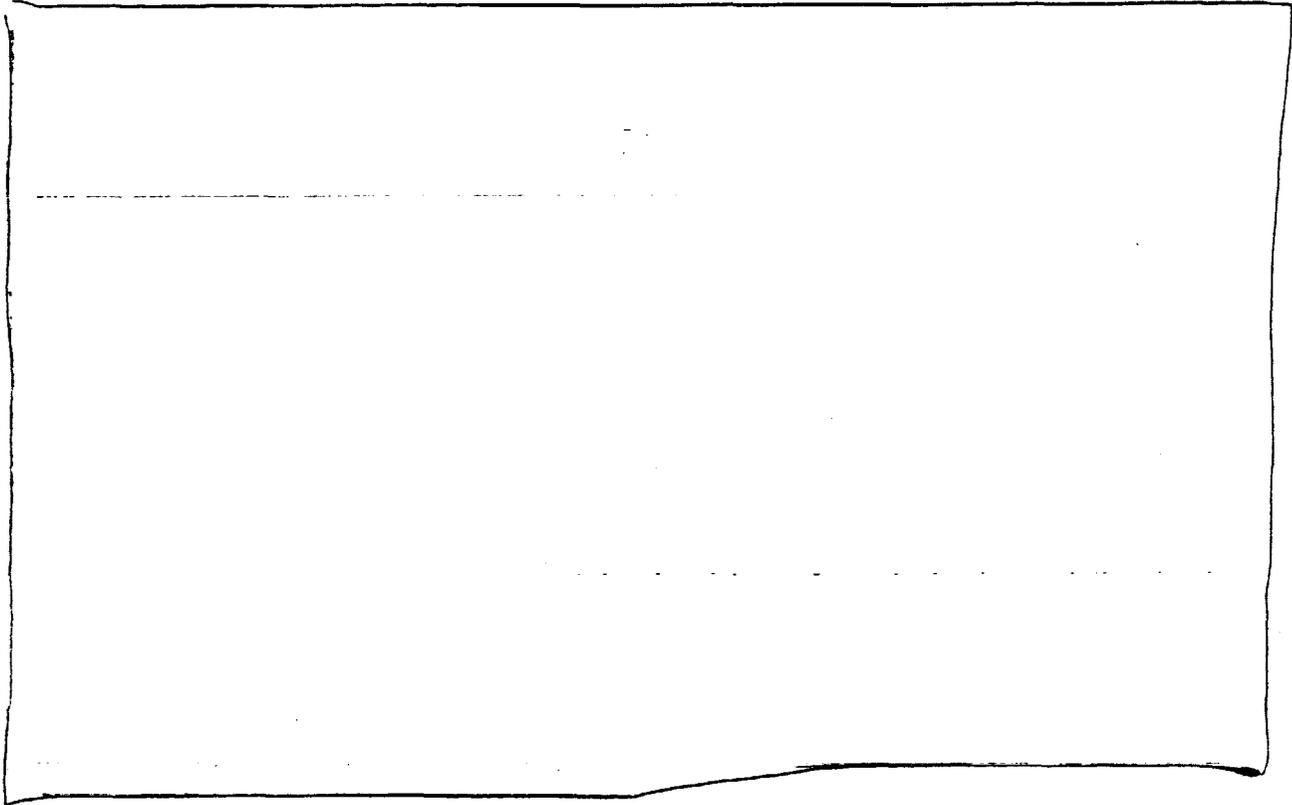
These data are more recent than the data from the original NDA presented in TABLE 1. Some species such as *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and methicillin-resistant *Staphylococcus* species have much higher MIC₉₀ values in the more recent studies. Resistance to fluoroquinolones has increased rapidly in these species.

As expected levofloxacin usually has MIC values that are about one dilution lower than those for ofloxacin. Levofloxacin is the L-isomer of ofloxacin and almost all of ofloxacin's antimicrobial activity resides in the L-isomer portion of the drug. All of the tested fluoroquinolones have lower MICs against the Gram-negative bacteria than they do against the Gram-positive bacteria. Norfloxacin has little if any activity against most Gram-positive bacteria. Ciprofloxacin generally is more active than the other tested quinolones against Gram-negative bacteria. Levofloxacin generally has slightly better activity than ciprofloxacin against the Gram-positive bacteria.

The sponsor has presented data from Phase III trials on many species with only one to three isolates found and tested. This is not enough data to determine what the true MIC₉₀ value is for these species. The Points to Consider Document issued by the Division of Anti-Infective Drug Products states that in order to be listed in the *in vitro* activity listing (list #2) in the package insert of the label at least 100 recent clinical isolates must be tested and the species must be a recognized pathogen in the disease that is being approved. The MIC₉₀ value must also be less than or equal to the drug's susceptible breakpoint. Since almost all data comes from the levofloxacin tablet NDA species listed in the tablet NDA in list #2 may be listed in this label if they are ocular pathogens. The species that will be allowed into list #2 are listed and discussed under the Package Insert section of this review.

MECHANISMS OF RESISTANCE STUDIES





PRECLINICAL EFFICACY (IN VIVO)

PHARMACOKINETICS/BIOAVAILABILITY

0.5% levofloxacin ophthalmic solution is to be dosed as one to two drops in the affected eye every 2 hours while awake up to 8 times per day on days 1 and 2 and then one to two drops every 4 hours while awake up to four times per day on days 3 through 5.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

The pharmacokinetics of levofloxacin in tear fluid has been assessed following ocular administration of 0.5% levofloxacin (Study 03-006). Subjects received one drop in each eye and had one tear sample collected from each eye at predetermined times. Samples were assayed using an HPLC method.

Pharmacokinetic analysis demonstrated that the mean levofloxacin concentration in human tears remained above 2 µg/mL for at least six hours post-dose. Mean levofloxacin concentrations in tears ranged from 34.9 µg/mL to 221.1 µg/mL during the 60 minute period following a single dose and the mean tear concentration measured 4 hours after a single dose was 17.04 ± 15.15 µg/mL. The mean value at 6 hours post-dose was 6.57 ± 5.26 µg/mL. The lower limit of the 95% confidence interval was 10.0 µg/mL for the two hour post-dose testing period and 1.9 µg/mL at four hours.

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

Santen performed three studies in ocular disease models to evaluate the efficacy of 0.5% levofloxacin ophthalmic solution against two of the most common organisms causing ocular infections, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

In the first study (25), levofloxacin and ofloxacin ophthalmic solutions were evaluated in the treatment of experimental endophthalmitis induced in rabbits by inoculating *Staphylococcus aureus* to the anterior chamber. The MIC value for the strain of *Staphylococcus aureus* used was 0.19 µg/mL for levofloxacin and 0.39 µg/mL for ofloxacin. The rabbits were divided into three groups: 1) treatment with topical 0.3% levofloxacin, 2) treatment with topical 0.3% ofloxacin, and 3) no treatment. The animals received three instillations of antimicrobial solution with 15 minute intervals between applications; 2 hours later, *Staphylococcus aureus* (1×10^4 cfu/mL) was inoculated to the anterior chamber. Ten hours after inoculation, topical antimicrobial agents were administered three times a day. The eyes were evaluated by slitlamp examination at 10, 24, 48, and 72 hours after inoculation. All animals in the untreated group developed severe inflammation and turbidity was seen all over the anterior chamber. In the treated groups no animal developed severe inflammation with turbidity all over the anterior chamber. In the levofloxacin group most of the inflammation seen was mild and two eyes did not develop any inflammation. The levofloxacin group appeared to do better than the ofloxacin group. Bacterial determination in aqueous humor taken at 10 hours after the bacterial inoculation showed no bacteria. This is probably due to the absence of bacteria in aqueous humor because they have been captured by neutrophils.

In the second study (26) the antibacterial efficacy of levofloxacin ophthalmic solution was evaluated against experimental endophthalmitis induced in rabbits by *Staphylococcus aureus* (2 to 5 x 10⁴ cfu/mL) injected into the vitreous. The levofloxacin MIC for the *S. aureus* strain used was 1.56 µg/mL. The rabbits were divided into two groups: 1) those treated with topical 3.0% levofloxacin, and 2) those treated with saline solution. Instillation was started just after bacterial inoculation. Each ophthalmic solution was administered 6x/day for 5 days. Observation of the inoculated eye was started 12 hours after bacterial inoculation (day 1) and was continued once every 24 hours for 108 hours (day 5). Corneal edema, turbidity in the anterior chamber and in the vitreous were observed using a slitlamp and indirect ophthalmoscope. In another experiment, three days after bacterial injection, the eyes were extracted under sterile conditions, and the vitreous liquid was aspirated from each eye. The liquid sample was incubated on normal agar plates for 48 hours to determine bacterial counts. In a third experiment, eyeballs were also extracted for histopathological inspection on day 3 and day 5 after bacterial inoculation.

Turbidity in the vitreous and in the anterior chamber appeared on day 2 in the control group and progressed with time in both groups. On day 3, corneal edema appeared in the control group and progressed with time. There was no difference between control and levofloxacin groups in corneal edema and vitreous turbidity. However, in the turbidity in the anterior chamber the levofloxacin group showed a milder degree of inflammation on day 3 and day 5. Bacterial colonies in the vitreous body on day 3 were less in the levofloxacin group (1.2×10^3 cfu) than in the control group (4.1×10^5 cfu). On day 3, mild turbidities in

the anterior chamber and the vitreous were observed in both groups. On day 5, prominent abscess formation, which fully filled the vitreous cavity, was seen in the control group. In contrast, in the levofloxacin group, turbidity of vitreous with marked infiltration of neutrophils was seen in the vitreous area contacting the retina and the ciliary body. Abscess formation in the retina could be seen in some eyes. Inflammation of the vitreous itself was slight or moderate. On day 3 and day 5 infiltration of inflammatory cells (mainly neutrophils) in the cornea and iris/ciliary body were observed in both groups, however, inflammation was milder in the levofloxacin group. On day 3, cell infiltration in the vitreous was mild in the levofloxacin group but severe in the control group. On day 5, in the levofloxacin group, cell infiltration in retina and swelling of the choroidal vein were seen, although the retinal structure was comparatively well preserved. In the control group, however, the retinal structure was markedly destroyed.

In the third study (27) the efficacy of levofloxacin ophthalmic solution and ointment as prophylactic agents against experimental *Pseudomonas aeruginosa* keratitis in rabbits was evaluated. Bacterial exposure on day 1 was followed starting 30 minutes after bacterial inoculation by drug administration 6 times a day on days 1 to 3, using the following: (1) 0.5% levofloxacin ophthalmic solution, (2) solution vehicle alone, (3) 0.5% levofloxacin ophthalmic ointment or (4) ointment vehicle alone. Daily clinical observation and corneal culture through day 6 showed that all corneas in the control groups were severely infiltrated with *P. aeruginosa*. In contrast, all corneas in the treatment groups remained free of infiltration and the cultures were negative.

In another study a 1.5% levofloxacin solution was compared to 0.3% ofloxacin solution and the levofloxacin vehicle against *Pseudomonas aeruginosa* ulcerative keratitis in rabbits. No organisms were recovered from infected eyes treated with levofloxacin or ofloxacin while approximately 10^4 cfu of *P. aeruginosa* was cultured from each cornea treated with vehicle.

In these studies treatment started shortly after bacterial inoculation. Levofloxacin treatment was always better than no treatment. It may be slightly better than ofloxacin treatment. No experiments were performed in which treatment started several days after the disease was present. Normally conjunctivitis treatment would start a few days after the disease occurs.

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ON 01/10/01

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

Two Phase III clinical trials are presented in this NDA.

Study 03-003—Phase III clinical and microbiological evaluation of 0.5% levofloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis.

Study 03-004—Phase III clinical and microbiological evaluation of 0.5% levofloxacin ophthalmic solution versus placebo for the treatment of bacterial conjunctivitis.

Conjunctival cul-de-sac swab specimens from patients enrolled in these studies were sent to an independent laboratory for bacterial culture and identification of genus and species of the potential pathogens. A total of 884 bacterial isolates, representing 70 distinct species, were obtained from 359 patients. From this group of isolates, 232 (103 Gram-negative and 129 Gram-positive) were selected to be tested for susceptibility to levofloxacin, ciprofloxacin, and ofloxacin. No more than 20 isolates of any one species were tested. Of the 103 Gram-negative organisms tested, 101 were tested by the [redacted] and 73 were tested by the [redacted] (MIC) method for susceptibility. Two Gram-negative isolates identified as *Acinetobacter lwoffii* lost viability during storage. All 129 Gram-positive isolates tested were tested by [redacted] and 113 were also tested by [redacted]

Levofloxacin breakpoints used in these studies were those determined for the systemic drug. It is important to keep in mind that levofloxacin breakpoints have not been correlated with clinical outcome for topical applications such as ophthalmic solutions. Because the amount of drug in tear fluids is usually much higher than what is achieved systemically, however, a "susceptible" isolate should be treated successfully. The use of levofloxacin MIC values allows the reviewer to determine if higher MIC values are associated with lower eradication rates of particular pathogens. In addition, assessing MIC values pre- and post-therapy allows us to determine whether treatment leads to an increase in MIC values. No MIC values were determined post-therapy, therefore, an assessment of whether treatment leads to increased MIC values can not be made.

Of the Gram-negative isolates tested, 99% were susceptible to levofloxacin by both the [redacted] (100/101) and the [redacted] (72/73). Only one Gram-negative isolate, a *Brevundimonas vesicularis*, was shown to be levofloxacin resistant (MIC value of 8 µg/mL) by both methods. This isolate was also resistant to ofloxacin (MIC = 16 µg/mL) and ciprofloxacin (MIC = 8 µg/mL). Ninety-four percent (94%) of the Gram-negative isolates (95/101) were susceptible to ciprofloxacin by the [redacted] and 95% (69/73) by the [redacted]. In addition to the levofloxacin-resistant isolate mentioned above, there were two other ciprofloxacin-resistant Gram-negative isolates, one strain each of *Klebsiella pneumoniae* (MICs = 2, 8, and 4 µg/mL for levofloxacin, ciprofloxacin, and ofloxacin, respectively) and *Stenotrophomonas maltophilia* (MICs of 2, 4, and 4 µg/mL for levofloxacin, ciprofloxacin, and ofloxacin, respectively). Ninety-six percent (96%) of the Gram-negative isolates were susceptible to ofloxacin

(97/101) by [redacted] and 70/73 by [redacted]. The ofloxacin-resistant isolates included the ciprofloxacin-resistant strains mentioned previously.

In regard to the Gram-positive isolates, 98% were susceptible to levofloxacin (127/129 by disk diffusion and 111/113 by broth dilution). Two of the 20 *Staphylococcus epidermidis* isolates tested were not susceptible to levofloxacin. One was shown to be resistant by both test methods, while the other was resistant by the [redacted] but had an intermediate breakpoint by the [redacted]. These same two non-susceptible strains of *S. epidermidis* were shown to be resistant to both ofloxacin and ciprofloxacin by both methods of testing. The first isolates had MICs of 4, 4, and 8 µg/mL for levofloxacin, ciprofloxacin, and ofloxacin, respectively. The second isolates had MICs of 16, ≥16, and 32 µg/mL for levofloxacin, ciprofloxacin, and ofloxacin, respectively.

Susceptibility to ciprofloxacin ranged from 61% (79/129 by [redacted]) to 82% (93/113 by [redacted]).

In addition to the two levofloxacin-resistant isolates four strains of *Streptococcus mitis* (MICs of 2, 4, 4 µg/mL; 2, 4, and 4 µg/mL; 2, 4 and 4 µg/mL; and 1, 2 (R by disk), and 2 µg/mL for levofloxacin, ciprofloxacin, and ofloxacin, respectively), two strains of *Streptococcus intermedius* (MICs of 2, 8, and 4 µg/mL and 2, 4, and 4 µg/mL, for levofloxacin, ciprofloxacin, and ofloxacin, respectively), five strains of *Streptococcus oralis* (MICs of 1, 2 [redacted] and 2 µg/mL; 2, 4, and 2 µg/mL; 2, 4, and 2 µg/mL; 1, 2 [redacted] and 2 µg/mL; and 1, 2, and 4 µg/mL for levofloxacin, ciprofloxacin and ofloxacin, respectively), and one strain of *Streptococcus pneumoniae* (MICs of 1, 1 (R by disk), and 2 µg/mL) were shown to be resistant to ciprofloxacin by the [redacted] and/or the [redacted].

Susceptibility to ofloxacin ranged from 78% (100/129 [redacted]) to 92% (104/113 [redacted]).

In addition to the two levofloxacin-resistant isolates, two strains of *Streptococcus mitis* were ofloxacin-resistant by the [redacted] but had an intermediate breakpoint by the [redacted] (MICs = 2, 4, 4 µg/mL and 2, 2, 4 µg/mL for levofloxacin, ciprofloxacin, and ofloxacin, respectively). A lot of the streptococci species are close to the susceptible breakpoint for each drug. This sometimes causes the species to be resistant by one method and susceptible or intermediate by the other method. There is a one-dilution error in the assay. Most of the streptococci are close to the susceptible breakpoint for each drug. Although the isolate may be susceptible to levofloxacin it is usually at or one dilution below the breakpoint. Ciprofloxacin has a breakpoint that is one dilution lower so if the MIC is the same it will be intermediate to ciprofloxacin. Most MICs are within one dilution of each other for all three drugs.

It appears that against the Gram-negative isolates all three drugs are about equal. Levofloxacin appears to be more active against the Gram-positive isolates than ciprofloxacin and may have a slight advantage against ofloxacin.

TABLE 3 shows the susceptibility results for the Gram-negative clinical isolates from the two Phase III trials. TABLE 4 shows the susceptibility results for the Gram-positive isolates.

TABLE 3
 Anti-Infective Susceptibilities for Gram-negative Organisms

Organism	LVFX			CPFX			OFLX			No. of Isolates
	% Susceptible	MIC ₉₀	MIC	% Susceptible	MIC ₉₀	MIC	% Susceptible	MIC ₉₀	MIC	
Gram-negative Isolates	DD	MIC	(µg/ml)	DD	MIC	(µg/ml)	DD	MIC	(µg/ml)	
Acinetobacter sp. (Total)	100 (18/18)	NT	NT	100 (18/18)	NT	NT	100 (18/18)	NT	NT	7
<i>A. baumannii</i>	100 (4/4)	NT	NT	100 (4/4)	NT	NT	100 (4/4)	NT	NT	4
<i>A. calcoaceticus</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>A. junii</i>	100 (2/2)	NT	NT	100 (2/2)	NT	NT	100 (2/2)	NT	NT	2
<i>A. lwoffii</i>	100 (11/11)	NT	NT	100 (11/11)	NT	NT	100 (11/11)	NT	NT	11*
Aeromonas sp.(Total)	100 (2/2)	100 (2/2)	0.03	100 (2/2)	100 (2/2)	0.015	100 (2/2)	100 (2/2)	0.06	2
<i>A. caviae</i>	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	≤0.008	100 (1/1)	100 (1/1)	≤0.03	1
<i>A. hydrophila</i>	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	0.06	1
<i>Alcaligenes xylosoxidans</i>	100 (2/2)	NT	NT	100 (2/2)	NT	NT	100 (2/2)	NT	NT	2
<i>Brevundimonas vesicularis</i>	0 (0/1)	0 (0/1)	8	0 (0/1)	0 (0/1)	8	0 (0/1)	0 (0/1)	16	1
<i>Chryseomonas luteola</i>	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	0.12	1
<i>Citrobacter freundii</i>	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.12	100 (1/1)	100 (1/1)	0.06	1
Enterobacter sp.(Total)	100 (4/4)	100 (4/4)	0.06	100 (4/4)	100 (4/4)	0.03	100 (4/4)	100 (4/4)	0.12	4
<i>E. aerogenes</i>	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	0.12	1
<i>E. agglomerans</i>	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	0.12	1
<i>E. cloacae</i>	100 (2/2)	100 (2/2)	0.06	100 (2/2)	100 (2/2)	0.03	100 (2/2)	100 (2/2)	0.12	2
<i>Escherichia coli</i>	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	0.06	1
<i>Flavimonas oryzihabitans</i>	100 (1/1)	100 (1/1)	0.12	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.25	1
<i>Flavobacterium gleum</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
Haemophilus sp.(Total)	100 (25/25)	100 (25/25)	0.03	100 (25/25)	100 (25/25)	0.03	100 (25/25)	100 (25/25)	0.06	25
<i>H. influenzae</i>	100 (20/20)	100 (20/20)	0.03	100 (20/20)	100 (20/20)	0.015	100 (20/20)	100 (20/20)	0.06	20
<i>H. parainfluenzae</i>	100 (5/5)	100 (5/5)	0.06	100 (5/5)	100 (5/5)	0.03	100 (5/5)	100 (5/5)	0.12	5
Klebsiella sp.(Total)	100 (5/5)	100 (5/5)	2	80 (4/5)	80 (4/5)	8	80 (4/5)	80 (4/5)	4	5
<i>K. oxytoca</i>	100 (2/2)	100 (2/2)	0.03	100 (2/2)	100 (2/2)	≤0.008	100 (2/2)	100 (2/2)	0.06	2
<i>K. pneumoniae</i>	100 (3/3)	100 (3/3)	2	67 (2/3)	67 (2/3)	8	67 (2/3)	67 (2/3)	4	3

*No growth for 2 isolates

DD – Disk Diffusion test

MIC – Broth Dilution test

TABLE 3 (Continued)
Anti-Infective Susceptibilities for Gram-negative Organisms

Organism Gram-negative Isolates	LVFX		CPFX			OFLX			No. of isolates	
	% Susceptible DD	MIC	MIC ₉₀ (µg/ml)	% Susceptible DD	MIC	MIC ₉₀ (µg/ml)	% Susceptible DD	MIC		MIC ₉₀ (µg/ml)
Moraxella sp.(Total)	100 (6/6)	100 (6/6)	0.06	100 (6/6)	100 (6/6)	0.06	100 (6/6)	100 (6/6)	0.12	6
<i>M. catarrhalis</i>	100 (5/5)	100 (5/5)	0.06	100 (5/5)	100 (5/5)	0.06	100 (5/5)	100 (5/5)	0.12	5
<i>M. osloensis</i>	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	≤0.008	100 (1/1)	100 (1/1)	0.06	1
Neisseria sp.(Total)	100 (4/4)	100 (4/4)	0.03	100 (4/4)	100 (4/4)	≤0.008	100 (4/4)	100 (4/4)	0.06	4
<i>N. mucosa</i>	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	≤0.008	100 (1/1)	100 (1/1)	0.06	1
<i>N. sicca</i>	100 (2/2)	100 (2/2)	0.03	100 (2/2)	100 (2/2)	≤0.008	100 (2/2)	100 (2/2)	0.06	2
<i>N. subflava</i>	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	≤0.008	100 (1/1)	100 (1/1)	0.06	1
<i>Chrobactrum anthropi</i>	100 (1/1)	100 (1/1)	0.5	0 (0/1)	100 (1/1)	0.25	0 (0/1)	100 (1/1)	0.5	1
<i>Pantoea agglomerans</i>	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	0.06	1
<i>Proteus mirabilis</i>	100 (5/5)	100 (5/5)	0.06	100 (5/5)	100 (5/5)	0.03	100 (5/5)	100 (5/5)	0.12	5
Pseudomonas sp.(Total)	100 (11/11)	100 (4/4)	0.5	91 (10/11)	100 (4/4)	0.12	91 (10/11)	100 (4/4)	1	11
<i>P. aeruginosa</i>	100 (3/3)	100 (3/3)	0.5	100 (3/3)	100 (3/3)	0.12	100 (3/3)	100 (3/3)	1	3
<i>P. cepacia</i>	100 (1/1)	100 (1/1)	0.03	100 (1/1)	100 (1/1)	0.015	100 (1/1)	100 (1/1)	0.12	1
<i>P. diminuta</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>P. fluorescens</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>P. paucimobilis</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>P. putida</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>P. stutzeri</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>P. vesicularis</i>	100 (2/2)	NT	NT	50 (1/2)	NT	NT	50 (1/2)	NT	NT	2
<i>Serratia marcescens</i>	100 (6/6)	100 (6/6)	0.25	100 (6/6)	100 (6/6)	0.12	100 (6/6)	100 (6/6)	0.5	6
<i>Sphingomonas paucimobilis</i>	100 (2/2)	100 (2/2)	0.12	100 (2/2)	100 (2/2)	0.25	100 (2/2)	100 (2/2)	0.25	2
<i>Stenotrophomonas maltophilia</i>	100 (3/3)	100 (3/3)	2	33 (1/3)	33 (1/3)	4	100 (3/3)	67 (2/3)	4	3
Total	99 (100/101)	99 (72/73)		94 (95/101)	95 (69/73)		96 (97/101)	96 (70/73)		101

DD – Disk Diffusion test

MIC – Broth Dilution test

TABLE 4
Anti-Infective Susceptibilities for Gram-positive Organisms

Organism	LVFX			CPFX			OFLX			No. of isolates
	% Susceptible	MIC	MIC ₉₀	% Susceptible	MIC	MIC ₉₀	% Susceptible	MIC	MIC ₉₀	
Gram-positive Isolates	DD	MIC	(µg/ml)	DD	MIC	(µg/ml)	DD	MIC	(µg/ml)	
Bacillus species	100 (1/1)	100 (1/1)	0.12	100 (1/1)	100 (1/1)	0.06	100 (1/1)	100 (1/1)	0.25	1
Corynebacterium sp. (Total)	100 (9/9)	NT	NT	78 (7/9)	NT	NT	89 (8/9)	NT	NT	9
<i>C. pseudodiphtheriticum</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>C. aquaticum</i>	100 (1/1)	NT	NT	0 (0/1)	NT	NT	0 (0/1)	NT	NT	1
<i>C. group ANF</i>	100 (1/1)	NT	NT	0 (0/1)	NT	NT	100 (1/1)	NT	NT	1
<i>C. group F</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>C. group G-1</i>	100 (4/4)	NT	NT	100 (4/4)	NT	NT	100 (4/4)	NT	NT	4
<i>C. xerosis</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>Enterococcus faecalis</i>	100 (2/2)	100 (2/2)	1	50 (1/2)	100 (2/2)	1	50 (1/2)	100 (2/2)	2	2
Micrococcus sp.(Total)	100 (6/6)	NT	NT	67 (4/6)	NT	NT	67 (4/6)	NT	NT	6
<i>M. luteus</i>	100 (4/4)	NT	NT	75 (3/4)	NT	NT	75 (3/4)	NT	NT	4
<i>M. lylae</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>M. varians</i>	100 (1/1)	NT	NT	0 (0/1)	NT	NT	0 (0/1)	NT	NT	1
Staphylococcus sp.(Total)	96 (47/49)	96 (46/48)	0.25	92 (45/49)	96 (46/48)	0.5	96 (47/49)	96 (46/48)	0.5	49
<i>S. aureus</i>	100 (18/18)	100 (18/18)	0.25	94 (17/18)	100 (18/18)	0.5	100 (18/18)	100 (18/18)	0.5	18
<i>S. capitis</i>	100 (1/1)	100 (1/1)	0.25	100 (1/1)	100 (1/1)	0.12	100 (1/1)	100 (1/1)	0.5	1
<i>S. epidermidis</i>	90 (18/20)	90 (18/20)	0.25	85 (17/20)	90 (18/20)	1	90 (18/20)	90 (18/20)	0.5	20
<i>S. haemolyticus</i>	100 (5/5)	100 (5/5)	0.25	100 (5/5)	100 (5/5)	0.25	100 (5/5)	100 (5/5)	0.5	5
<i>S. hominis</i>	100 (3/3)	100 (3/3)	0.12	100 (3/3)	100 (3/3)	0.12	100 (3/3)	100 (3/3)	0.25	3
<i>S. simulans</i>	100 (1/1)	100 (1/1)	0.25	100 (1/1)	100 (1/1)	0.25	100 (1/1)	100 (1/1)	0.5	1
<i>S. warneri</i>	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
<i>Stomatococcus mucilaginosus</i>	100 (2/2)	100 (2/2)	0.25	0 (0/2)	100 (2/2)	0.5	100 (2/2)	100 (2/2)	0.5	2

DD - Disk Diffusion test

MIC - Broth Dilution test

TABLE 4 (Continued)
Anti-Infective Susceptibilities for Gram-positive Organisms

Organism Gram-positive Isolates	LVFX		MIC ₉₀ (µg/ml)	CPFX		MIC ₉₀ (µg/ml)	OFLX		MIC ₉₀ (µg/ml)	No. of isolates
	% Susceptible DD	MIC		% Susceptible DD	MIC		% Susceptible DD	MIC		
Streptococcus sp.(Total)	100 (60/60)	100 (60/60)	2	37 (22/60)	70 (42/60)	4	62 (37/60)	88 (53/60)	4	60
<i>S. adjacens</i>	100 (1/1)	100 (1/1)	1	0 (0/1)	100 (1/1)	2	0 (0/1)	100 (1/1)	2	1
<i>S. agalactiae</i>	100 (1/1)	100 (1/1)	1	0 (0/1)	100 (1/1)	1	100 (1/1)	100 (1/1)	2	1
<i>S. anginosus</i>	100 (1/1)	100 (1/1)	1	100 (1/1)	100 (1/1)	1	100 (1/1)	100 (1/1)	2	1
<i>S. bovis</i>	100 (1/1)	100 (1/1)	1	0 (0/1)	0 (0/1)	2	0 (0/1)	100 (1/1)	2	1
<i>S. constellatus</i>	100 (1/1)	100 (1/1)	0.5	100 (1/1)	100 (1/1)	0.5	100 (1/1)	100 (1/1)	1	1
<i>S. gordonii</i>	100 (2/2)	100 (2/2)	0.5	100 (2/2)	100 (2/2)	0.5	100 (2/2)	100 (2/2)	1	2
<i>S. intermedius</i>	100 (3/3)	100 (3/3)	2	33 (1/3)	33 (1/3)	8	33 (1/3)	33 (1/3)	4	3
<i>S. mitis</i>	100 (14/14)	100 (14/14)	2	21 (3/14)	50 (7/14)	4	50 (7/14)	71 (10/14)	4	14
<i>S. oralis</i>	100 (11/11)	100 (11/11)	2	18 (2/11)	36 (4/11)	4	36 (4/11)	91 (10/11)	2	11
<i>S. pneumoniae</i>	100 (19/19)	100 (19/19)	1	58 (11/19)	95 (18/19)	1	89 (17/19)	100 (19/19)	2	19
<i>S. pyogenes</i>	100 (1/1)	100 (1/1)	0.5	0 (0/1)	100 (1/1)	0.25	100 (1/1)	100 (1/1)	1	1
<i>S. salivarius</i>	100 (5/5)	100 (5/5)	1	20 (1/5)	100 (5/5)	1	40 (2/5)	100 (5/5)	2	5
Total	98 (127/129)	98 (111/113)		61 (79/129)	82 (93/113)		78 (100/129)	92 (104/113)		129

DD – Disk Diffusion test

MIC – Broth Dilution test

APPEARS THIS WAY
ON ORIGINAL

TABLE 5 compares the susceptibility results for the most common isolates from the Phase III clinical trials.

TABLE 5
 Comparison of Susceptibility in Phase III trials for most Common Pathogens

Organism	Method	LVFX No. Susceptible/ No. tested	CPFX No. Susceptible/ No. tested	OFLX No. Susceptible/ No. tested
<i>A. lwoffii</i>		11/11 (100%)	11/11 (100%)	11/11 (100%)
		N/A	N/A	N/A
<i>H. influenzae</i>		20/20 (100%)	20/20 (100%)	20/20 (100%)
		20/20 (100%)	20/20 (100%)	20/20 (100%)
<i>Pseudomonas sp.</i>		11/11 (100%)	10/11 (91%)	10/11 (91%)
		4/4 (100%)	4/4 (100%)	4/4 (100%)
<i>S. aureus</i>		18/18 (100%)	17/18 (94%)	18/18 (100%)
		18/18 (100%)	18/18 (100%)	18/18 (100%)
<i>S. epidermidis</i>		18/20 (90%)	17/20 (85%)	18/20 (90%)
		18/20 (90%)	18/20 (90%)	18/20 (90%)
<i>Streptococcus sp.</i>		60/60 (100%)	22/60 (37%)	37/60 (62%)
		60/60 (100%)	42/60 (70%)	53/60 (88%)
<i>S. mitis</i>		14/14 (100%)	3/14 (21%)	7/14 (50%)
		14/14 (100%)	7/14 (50%)	10/14 (71%)
<i>S. oralis</i>		11/11 (100%)	2/11 (18%)	4/11 (36%)
		11/11 (100%)	4/11 (36%)	10/11 (91%)
<i>S. pneumoniae</i>		19/19 (100%)	11/19 (58%)	17/19 (89%)
		19/19 (100%)	18/19 (95%)	19/19 (100%)

TABLE 6 shows the eradication rates by organisms for the levofloxacin treated pathogens isolated in the two Phase III clinical trials.

APPENDIX
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TABLE 6
 Microbial Eradication Rates at Final by Organism

Organism	Treatment		
	0.5% LVFX N ¹ (%)	0.3% OFLX N ¹ (%)	Placebo N ¹ (%)
Gram-negative isolates			
Enterobacter/Pantoea	1/1(100.0)		1/1(100.0)
<i>Escherichia coli</i>	1/1(100.0)		
<i>Proteus mirabilis</i>	3/3(100.0)		1/1(100.0)
<i>Serratia marcescens</i>	4/4(100.0)	1/1(100.0)	1/1(100.0)
Haemophilus	52/56(92.9)	33/37(89.2)	12/23(52.2)
<i>H. influenzae</i>	49/53(92.5)	32/36(88.9)	12/23(52.2)
<i>H. parainfluenzae</i>	3/3(100.0)	1/1(100.0)	
Other Neisseria	1/1(100.0)	1/1(100.0)	
Moraxella	1/1(100.0)		1/1(100.0)
Acinetobacter	6/7(85.7)	3/4(75.0)	3/3(100.0)
Pseudomonas	6/6(100.0)	2/3(66.7)	
<i>P. aeruginosa</i>		0/1(0.0)	
Other Ps./Other Non-Enterobacteriaceae	6/6(100.0)	2/2(100.0)	
Total Gram-negative isolates	75/80(93.8)	40/46(87.0)	19/30(63.3)
Gram-positive isolates			
Corynebacterium	5/5(100.0)	2/2(100.0)	
Staphylococcus	49/49(100.0)	36/36(100.0)	14/15(93.3)
<i>S. aureus</i>	24/24(100.0)	19/19(100.0)	5/6(83.3)
<i>S. epidermidis</i>	22/22(100.0)	15/15(100.0)	7/7(100.0)
Other coagulase negative Staphylococcus	3/3(100.0)	2/2(100.0)	2/2(100.0)
Micrococcus/Stomatococcus	4/4(100.0)	1/1(100.0)	1/1(100.0)
Streptococcus	61/69(88.4)	22/30(73.3)	13/23(56.5)
Streptococcus, Group A, β hemolytic (<i>S. pyogenes</i>)	1/1(100.0)		
<i>S. pneumoniae</i>	45/53(84.9)	17/25(68.0)	9/19(47.4)
Other Streptococcus (Groups D, G: non-grouped; viridans)	15/15(100.0)	5/5(100.0)	4/4(100.0)
Total Gram-positive isolates	119/127(93.7)	61/69(88.4)	28/39(71.8)
Total isolates	194/207(93.7)	101/115(87.8)	47/69(68.1)

¹Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline

Most species had only one or two isolates represented in the clinical trials. Usually 10 or more isolates must have been found in clinical trials to place the species in the label. Classifications such as "other Pseudomonas/Other Non-Enterobacteriaceae" are not usually allowed in the label since this is a very broad category and usually only species or in a few exceptional cases, such as *Peptostreptococcus* or *Shigella*, genera are allowed to be listed. The following species had 10 or more isolates in the clinical trials:

Acinetobacter lwoffii
Haemophilus influenzae
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus mitis
Streptococcus oralis

We have often allowed the classifications of Streptococci (Group C/F), Streptococci (Group G), and Viridans group streptococci in the label. I believe that this is justified for this product.

The final list of organisms that is allowed into the label will follow what the Medical Officer lists in the Indications and Usage section of the label.

The sponsor has listed every organism that was found in the clinical trials in the *in vitro* activity only (list #2) of the Microbiology subsection. This is not acceptable. In order to be listed at least 100 isolates must have been tested in at least two separate studies. Over 75 of the 100 isolates must be from geographically diverse areas of the United States. The listed species must also have an MIC₉₀ value less than the systemic susceptible breakpoint for the drug and must be a pathogen in an indication that the drug is being approved for. The organisms that will be allowed into list #2 are discussed below in the Package Insert section of this review.

PACKAGE INSERT

The applicant's proposal for the following Microbiology subsection for the package insert is listed below. This reviewer feels that since the proposal is based on the systemic drug label, the opening paragraphs should be identical to the systemic drug label. The applicant's statement "Levofloxacin demonstrates statistically superior overall *in vitro* efficacy compared to other fluoroquinolones..." is not entirely true. Many of the newer fluoroquinolones have much better *in vitro* activity than does levofloxacin. Ciprofloxacin usually has lower MIC values than levofloxacin against most Gram-negative bacteria. This statement must be deleted. The sponsor has based this statement on a few isolates in their clinical trials and compared levofloxacin only to ciprofloxacin and ofloxacin. The statement "Although cross-resistance has been observed between levofloxacin and other fluoroquinolones, some microorganisms, such as *Staphylococcus aureus* and some Streptococcus species, that are resistant to other fluoroquinolones may be susceptible to levofloxacin" is misleading. The sponsor has only compared levofloxacin to ciprofloxacin, which does not have very good Gram-

6 *pages of revised draft
labeling have been
redacted from this portion
of the document.*

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