CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-199

MEDICAL REVIEW

Medical Officer's Review of NDA 21-199
Original

NDA # 21-199		Submission:	2/28/2000
M.O. Review #1		Review completed:	7/21/2000

Proposed trade name:	QUIXIN™
Generic name:	levofloxacin hemihydrate ophthalmic solution, 0.5%
Sponsor:	Santan Inc. Napa, CA 94558
Pharmacologic Category:	Anti-infective (fluoroquinolone)
Proposed Indication(s):	Bacterial conjunctivitis
Dosage Form:	Ophthalmic solution
Route(s) of Administration:	Topical ophthalmic administration
NDA Drug Classification:	3 P
Related Drugs:	Ofloxacin ophthalmic solution Ciprofloxacin ophthalmic solution Norfloxacin ophthalmic solution
Related INDs:	[redacted] Levofloxacin ophthalmic solution (Santan)
Related NDAs:	NDA 20-634 Levaquin Tablets (levofloxacin tablets) NDA 20-635 Levaquin Injection

2 Table of Contents

3 Material Reviewed

NDA Volumes 1.1, 1.17-1.45

4 Chemistry/Manufacturing Controls

Composition of Levofloxacin Ophthalmic Solution, 0.5% (Formula 1014S)

Ingredient	Percent (w/v)	Quantity (mg/mL)
Levofloxacin hemihydrate[1]	0.512	5.12
Benzalkonium chloride,[2] NF/EP	0.0050	0.050
Sodium chloride, USP/EP	[redacted]	[redacted]
Hydrochloric acid, NF/EP and/or Sodium hydroxide, NF/EP	[redacted]	
Purified water,[3] USP/EP	[redacted]	

[1] Each mL contains 5 mg levofloxacin equivalent to 5.12 mg levofloxacin hemihydrate (adjusted to 100% potency).
[2] Added by assay value to achieve target BAK concentration.
[3] A higher grade of water may be used.

Reviewer's Comments: [redacted]

Drug Product Specifications

Specification	Limit
Appearance	Solution: Clear, light yellow to light greenish-yellow solution, practically free of visible particulate matter Clarity and Degree of Opalescence: Degree of opalescence ≤ Reference Suspension I Degree of Coloration: Solution Color≤ Reference Solution GY_3

*Performed at release.

Reviewer's Comments: *Acceptable, except that unidentified impurities should be limited to no more than 0.1%.*

Container/Closure

Drug product is supplied in a white low-density polyethylene plastic bottle with a natural clear low-density polyethylene dropper tip and a tan high density polyethylene screw cap. It will be provided in both 2.5mL and 5mL fill sizes.

Reviewer's Comments: *Acceptable.*

Special stability information

In addition to the long-term and accelerated stability studies, photostability and temperature stress testing were performed on the drug product.

Results from the photostability testing were within specifications, and there were no statistically significant differences between the test results for the control samples and the samples exposed to light, indicating that the product does not require special label instructions to "protect from light".

Results from the temperature stress testing were within specifications and there were no statistically significant differences between the cycled samples and the control samples. The results indicate that the stability of the drug product is not affected by short-term excursions to freezing conditions and therefore the product does not require labeling to "protect from freezing".

APPEARS THIS WAY
ON ORIGINAL

5 Animal Pharmacology/Toxicology

Target organ toxicity that has been associated with quinolone administration in animals includes articular cartilage lesions, decreased neutrophil counts, prolonged cardiac repolarization, and a blocking effect on neuromuscular transmission. Studies and literature support LVFX as having either no greater toxicity than other marketed quinolones, or in some cases, less toxicity than other marketed quinolones.

Levofloxacin has a high affinity for melanin, and after an ophthalmic dose, levofloxacin concentrates in the ocular tissues with a high melanin content, the iris/ciliary body and the RPE/choroid. These concentrations are maintained for 3 to 6 months after a single dose

Systemic distribution of LVFX in the rat was minimal following ophthalmic administration of a single dose. The low levels of drug present in plasma were accompanied by similarly low levels in all of the other systemic organs/tissues tested, with the kidney, duodenum, and ileum showing the highest concentrations. By 3 to 4 days post-treatment, essentially all of the administered dose had been excreted in either urine (~45%) or feces (~55%).

Reviewer's Comments: *NDA 19-992, Ciprofloxacin ophthalmic solution included studies which demonstrated that ophthalmic administration of fluoroquinolones did not achieve sufficient systemic levels to affect the development of weight bearing joints.*

6 Clinical Background

A number of ophthalmic fluoroquinolones (ciprofloxacin, norfloxacin and ofloxacin) have been approved for use in the treatment of bacterial conjunctivitis. Although the precise mechanism of action responsible for the bactericidal effects of the quinolones is not fully understood, it is known that fluoroquinolones bind to both DNA and the α-subunit of DNA gyrase (a topoisomerase II comprised of two alpha and two beta subunits). This interaction forms a ternary complex, which interferes with enzyme-mediated processing of DNA and ultimately inhibits normal replicative and transcriptional activity. Levofloxacin is the L-enantiomer of the racemic ofloxacin and has been shown *in vitro* to demonstrate anti-infective activity against a broad spectrum of Gram-positive and Gram-negative bacteria.

6.2 Important information from related INDs and NDAs –*see Section 6.3.*

6.3 Foreign experience

The first worldwide approval of levofloxacin was an oral tablet formulation in Japan (Daiichi, Cravit™). Levofloxacin is now widely available throughout Europe, Asia and the Americas.

The drug substance was obtained by license for ophthalmic use from Daiichi Pharmaceutical Co., Ltd. (Daiichi) in Japan. Daiichi also licensed the compound to the Robert Wood Johnson Pharmaceutical Research Institute (RW Johnson) in the US for systemic use. The RW Johnson NDAs 20-634 and 20-635 for Levaquin® Tablets and Levaquin® Injection are approved. Santen has permission to cross-reference these NDAs in support of this application.

Ortho-McNeil Inc., a subsidiary of RW Johnson, markets systemic formulations under the tradename Levaquin® in the US. markets systemic formulations for infection in Europe under the trade name Tavanic®.

Santen Pharmaceutical, Co., Ltd. recently received approval in Japan for a 0.5% levofloxacin ophthalmic solution formulated without the preservative benzalkonium chloride. The product will be marketed under the tradename Cravit™.

APPEARS THIS WAY
ON ORIGINAL

The drug substance has been marketed in the following countries:

Aruba	Guatemala	Paraguay
Austria	Haiti	Peru
Brazil	Hong Kong	Philippines
Canada	Hungary	Portugal
Chile	India	Singapore
China	Indonesia	South Africa
Colombia	Ireland	Spain
Costa Rica	Italy	Sweden
Curacao	Jamaica	Switzerland
Dominican Republic	Japan	Thailand
Ecuador	Korea	Turkey
Egypt	Malaysia	UK
El Salvador	Mexico	Uruguay
Finland	Netherlands	USA
Germany	Nicaragua	Venezuela
Greece	Pakistan	

The drug has not been withdrawn from marketing in any country for any reason related to safety or effectiveness.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Summary of Ophthalmic Clinical Studies in Japan

Reference (Phase)	Design/Duration	Study Population	Number of Subjects Enrolled 0.5% LVFX	0.3% LVFX	0.3% OFLX
95034 (I)	Double-masked, 2 drops, 2 weeks, q.i.d.	Normal	10[a]	10[a]	
97002 (II)	Double-masked, parallel, 2 drops, 2 weeks, t.i.d.	External Ocular Infections	86	87	79
97051 (II)	Open-label, 1 drop, 2 days, 6 times a day	Patients Undergoing Ocular Surgery	75		
97031 (III)	Double-masked, parallel, 2 drops, 2 weeks, t.i.d.	External Ocular Infections	180		186
97070 (III)	Open-label, parallel, 1 drop, 2 weeks, t.i.d.	External Ocular Infections	152		
TOTAL			**503**	**97**	**265**

[a] The same 10 volunteers received 0.3% and 0.5% LVFX

These clinical trials showed that levofloxacin ophthalmic solution administered t.i.d. for 2 weeks is effective and safe in the treatment of external ocular infections. Of the more than 500 patients who were judged evaluable for safety, adverse reactions were all mild or moderate in severity.

Reviewer's Comments: *These studies contribute to the safety database, but are not the primary support of efficacy.*

APPEARS THIS WAY
ON ORIGINAL

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Summary of Ocular Pharmacokinetic and Biopharmaceutic Studies

Study No.	Study Design	No. of Subjects	Dose per eye	Results
03-005[1]	Days 1 & 16 q.d. Days 2–3 8x/day (q 2h) Days 4–15 q.i.d. (q 4h) Collection of plasma samples on Days 1, 4, 6, & 15.	15 healthy adults	2 drops of 0.5% levofloxacin	The mean $AUC_{(0\text{-}6h)}$ on Day 1 was 5.01 ng•hour/mL (±2.04) compared to 12.06 ng•hour/mL (±5.36) on Day 15. The mean C_{max} on Day 1 was 0.94 ng/mL (±0.47) compared to 2.15 ng/mL (±1.00) on Day 15.[3] T_{max} occurred slightly later on Day 15 (0.93 hours) relative to Day 1 (0.64 hours).
03-006[1]	Day 1 q.d Collection of tear samples at times up to 24 hours postdose; one tear sample collected from each eye.	30 healthy adults	1 drop of 0.5% levofloxacin	C_{max} = 221.06 ±256.68 μg/mL at 15 min postdose. Mean tear fluid levofloxacin concentrations remained above 2 μg/mL for at least 6 hrs postdose, with tear concentrations ≥ 2 μg/mL in 5 of 6 patients at 4 hrs postdose.
95034[2]	1 day, q.d., 2 weeks, q.i.d. Subjects randomized to receive 0.5% eye drops in one eye, 0.3% in other eye. Collection of serum samples 1 hr after mid-day dose on last day of dosing.	10 healthy males	2 drops of 0.5% or 0.3% levofloxacin	Levofloxacin not measurable in serum after 14 days of q.i.d. dosing, with assay limit of detection < 10 ng/mL.

1 Proposed US Formulation
2 0.5% Levofloxacin Ophthalmic Solution (no preservative)
3 The marketed oral 500-mg dosage of levofloxacin provides a mean peak plasma levofloxacin concentration of 5.1 μg/mL after a single dose.

Plasma Levels

The potential for systemic exposure following topical ocular administration of 0.5% LVFX was investigated in Study 03-005. The mean levofloxacin concentration in plasma 1 hour post dose ranged from 0.86 ng/mL on Day 1 to 2.05 ng/mL on Day 15. Maximum levofloxacin concentration increased from 0.94 ng/mL on Day 1 to 2.15 ng/mL on Day 15 after dosing for 15 days. The highest maximum mean levofloxacin concentration of 2.25 ng/mL was measured on Day 4 following two days of dosing every two hours.

Tear Fluid Levels

The pharmacokinetics of levofloxacin in tear fluid has been assessed following ocular administration of 0.5% LVFX. 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. Mean levofloxacin concentrations in tears ranged from 34.9 to 221.1 μg/mL during the 60 minutes period following a single dose and the mean tear concentration measured 4 hours after a single ophthalmic dose was 17.04 μg/mL.

6.6 Proposed Directions for Use

The proposed dosing regimen is one to two drops every 2 hours while awake (up to 8 times per day) on Days 1 and 2 and one to two drops every 4 hours while awake (up to 4 times per day) on Days 3 through 5.

7 Description of Clinical Data Sources

Study No.	Start Date Phase	Study Design/ Patient Population	Patients entering / receiving / completing treatment	Age Range (mean)	Sex M/F (%)	Race C/NC (%)
03-002	May 1997 Phase 2	Randomized, double-masked, parallel-group, active-controlled, multicenter in patients with bacterial conjunctivitis or blepharoconjunctivitis	LVFX 23/23/16 OFLX 23/23/18	2-83 (28.65) 5-91 (42.48)	6/17 (26/74) 5/18 (22/78)	17/6 (74/26) 21/2 (9/91)
03-003	March 1998 Phase 3	Randomized, double-masked, parallel-group, active controlled, multicenter in patients with bacterial conjunctivitis	LVFX 211/207/197 OFLX 212/206/191	1-80 (31.20) 1-91 (32.75)	80/127 (39/61) 74/132 (36/64)	156/51 (75/25) 152/54 (74/26)
03-004	March 1998 Phase 3	Randomized, double-masked, parallel-group, placebo-controlled, multi-center in patients with bacterial conjunctivitis	LVFX 126/124/115 VEHC 123/120/112	2-91 (34.47) 2-86 (33.83)	46/78 (37/63) 59/61 (49/51)	94/30 (76/24) 94/26 (78/22)
03-001	Mar. 1996 Phase 1	Randomized, investigator-masked, contralateral eye-controlled, single-center safety study in healthy adults with asymptomatic eyes	LVFX 26/26/26	23-74 (45.12)	7/19 (27/73)	16/10 (62/38)

Demographic information (age, sex, and race) is presented for subjects receiving study medications.
0.5% LVFX = 0.5% levofloxacin M/F = Male/Female
0.3% OFLX = 0.3% ofloxacin C/NC = Caucasian/Non-Caucasian

APPEARS THIS WAY
ON ORIGINAL

8 Clinical Studies

8.1 Indication #1 Bacterial Conjunctivitis

8.1.1 Reviewer's Trial # 1 Sponsor's protocol # 03-003

8.1.1.1 Objective/Rationale

The objective of this study was to evaluate the clinical and microbial efficacies, and safety of 0.5% levofloxacin ophthalmic solution (0.5% LVFX) compared to 0.3% ofloxacin ophthalmic solution (0.3% OFLX) for the treatment of bacterial conjunctivitis in adults and children one year of age and older.

8.1.1.2 Design

Multicenter, randomized, active-controlled, double-masked comparison of 0.5% LVFX versus 0.3% OFLX in patients with bacterial conjunctivitis.

8.1.1.3 Protocol

Enrolled patients dosed with masked study medication for 5 days. Patients instilled one to two drops in the infected eye(s) every two hours, up to 8x/day, while awake on Days 1 and 2, then one to two drops every four hours, up to 4x/day, while awake on Days 3 through 5. The patients were examined at Visit 1 (Day 1), Visit 2 (Day 3+1), and Visit 3 (Day 7±1). At each visit, patients underwent routine ophthalmic exams, including visual acuity (BCVA) and biomicroscopy. In addition, at Visit 1 and Visit 3 (and/or Visit 2 if they were clinically worse or discontinued early), the patients had a fundus exam. At each visit microbial cultures were taken of the bulbar and palpebral conjunctiva from the infected eye(s).

At Visit 2, the investigators recorded their clinical impression of the patient's infected eye(s) based on change from baseline in ocular discharge and bulbar and palpebral conjunctival injection. If the patient exhibited a clinical worsening of conjunctival discharge and redness from baseline, the patient was to be exited from the study.

Visit 3, the off-therapy exit examination, was conducted on Day 7±1 after patients had last used their study medication on Day 5. As was done at Visit 2, the investigators recorded their clinical impression of the patient's infected eye(s) and, after undergoing the appropriate biomicroscopy and dilated ophthalmoscopy examinations, the patient was exited from the study.

Some patients may have had only one eye with positive clinical and microbial baseline evaluations while others may have had bilaterally positive clinical and microbial evaluations at baseline. For the purposes of the primary analyses of efficacy data, the analysis eye was determined in a stepwise manner as follows:

- The eye with positive clinical and microbial baseline evaluations if only one eye had both clinical and microbial evaluations positive at baseline.
- The eye with the highest combined ocular discharge and redness scores at baseline if the patient was bilaterally positive for both clinical and microbial baseline evaluations. The combined ocular discharge and redness score were computed for each eye as the sum of the Day 1 values for conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection.
- The right eye if the patient was bilaterally positive for both clinical and microbial baseline evaluations and had equal baseline ocular discharge and redness scores in both eyes.

Investigators

Abelson, M	863 Turnpike Street, Suite 224, North Andover, MA 01845 555 Turnpike St., North Andover, MA 01845 138 Haverhill St., Andover, MA 01810
Bahadur, G	The Sinskey Eye Institute, 2232 Santa Monica Blvd., Santa Monica, CA 90404
Braunstein, R	Harkness Eye Institute, 635 W. 165th St., Box 39, New York, NY 10032 16 East 60th St., Suite 420, New York, NY 10022
Caine, R	110 Cambridge St., Fredericksburg, VA 22405
Cavanaugh	The Hunkeler Eye Center, 43321 Washington, Suite 6000, Kansas City, MO 64111 Hunkeler Eye Study Center, 4320 Wornall Suite 520, Kansas City, MO 64111
Dell, S	Texan Eye Care, 1700 S. Mopac, Austin, TX 78746 Texan Eye Care, 1020 W. 34th Street, Austin, TX 78705
Donshik, P	29 N. Main Street, West Hartford, CT 06197-1933 54 W. Avon Road, West Hartford, CT 06001
Friedlaender, M	Scripps Clinic and Research Foundation, MS 214, 10666 N. Torrey Pines Road La Jolla, CA 92037
Lichtenstein, S	Metro United Way Building , Suite 325, 334 East Broadway, Louisville, KY 40202
Levy, N	Florida Ophthalmic Institute, 7100 NW 11th Place, Gainesville, FL 32605-3192
McCulley, J	UT Southwestern Medical Center – Dallas, Department of Ophthalmology, 5323 Harry Hines Blvd., Dallas, TX 75235-9057 Parkland Memorial Hospital, 5201 Harry Hines Blvd., Dallas, TX 75235 Children's Med. Ct. of Dallas, 1935 Motor St., Dallas, TX 75235
Milstein, B	The Eye Clinic of Texas, 2302 Avenue P, Galveston, TX 77550
Moran, C Jr.	Kentucky Eye Care, 6400 Dutchmans Parkway, Suite #125, Louisville, KY
Mundorf, T	Presbyterian Medical Tower, 1718 E. 4th Street, Suite 902, Charlotte, NC 29204
O'Brien, T	JHH-Wilmer Eye Institute, 600 North Wolfe Street, Baltimore, MD 21287-9121 JHH-Greenspring Station, 10753 Falls Rd., Suite 305, Lutherville, MD 21093
Prepas, S	1401 Avocado Ave., Suite 708, Newport Beach, CA 92660 21320 Hawthorne Blvd., Suite 104, Torrance, CA 90503
Reidy, R	806 Martin Luther King Jr. Avenue NE, Albuquerque, NM 87102-3675
Robin, S	St. Paul-Ramsey Clinic, 640 Jackson Street, St. Paul, MN 55101
Sall, K	9604 Artesia Blvd., Suite 203, Bellflower, CA 90706
Schwab, I Mannis, M	Department of Ophthalmology, Univ. of California Davis, 1603 Alhambra Blvd., Sacramento, CA 95816 Ellison Ambulatory Care Center, 4860 Y Street, Suite 2400,Sacramento, CA 95817
Sugar, A	Kellogg Eye Center, Univ. of Michigan, 1000 Wall Street, Ann Arbor, MI 48105-1994
Valluri, S	Indiana University, 702 Rotary Circle, Indianapolis, IN 46202 550 N. University Blvd., Suite 3005-3073, Indianapolis, IN 46202
Wapner, F	Advanced Eye Care, 1250 E 3900 South, #310, Salt Lake City, UT 84124
Wolfe, T	Dean McGee Eye Institute, 608 Stanton Young Blvd., Oklahoma City, OK 73104

Reviewer's Comments: *Financial disclosure statement has been reviewed.*

8.1.1.3.1 Population

A sufficient number of patients were to be enrolled to obtain approximately 200 culture positive patients, including children 1 year of age and older, meeting all eligibility requirements and exhibiting ocular discharge and redness.

8.1.1.3.2 Endpoints

Primary Clinical Efficacy

Outcome (0-3)	Cardinal Signs*	Definition	
Resolved (0)	Absence	Cure	Success
Improved (1)	At least a 1 unit improvement from baseline	Non-resolved	
No Change (2)	No overall response from baseline		Failure
Worse (3)	At least a 1 unit worsening from baseline		

* Conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection

Primary Microbial Efficacy

Outcome (0-3)	Baseline Organisms*	Definition	
Resolved (0)	Absence, no growth	Eradication	Success
Improved (1)	Reduction below pathogenic criteria	Non-resolved	
No Change (2)	No response or overall improvement		Failure
Worse (3)	Increase		

*Change in colony forming units (CFUs) from baseline

Reviewer's Comments: *Bacterial conjunctivitis is generally is a self limited disease which improves over time. Only resolution is an acceptable endpoint (for both clinical and microbial efficacy).*

APPEARS THIS WAY
ON ORIGINAL

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Summary of Demographics

	Per Protocol		All Patients		
	0.5% LVFX	0.3% OFLX	0.5% LVFX	0.3% OFLX	P-VALUE[1]
Number of Patients:	109	99	211	212	
AGE					0.7471
MEAN(SD)	29.3 (23.0)	28.2 (23.1)	31.1 (20.8)	32.5 (21.2)	
MEDIAN	26	24	31	30	
MIN-MAX	1-80	1-79	1-91	1-91	
>16 years	67 (61%)	62 (63%)	154 (73%)	159 (75%)	
12-16 years	7 (6%)	6 (6%)	11 (5%)	12 (6%)	
2-11 years	30 (27%)	26 (26%)	39 (18%)	34 (16%)	
<2 years	5 (5%)	5 (5%)	7 (3%)	7 (3%)	
SEX: N(%)					0.8752
Female	66 (60.6)	61 (61.6)	130 (61.6)	137 (64.6)	
Male	43 (39.5)	38 (38.4)	81 (38.4)	75 (35.4)	
RACE: N(%)					0.6223
Caucasian	89 (81.7)	76 (76.8)	159 (75.4)	155 (73.1)	
Black	7 (6.42)	11 (11.11)	22 (10.4)	26 (12.3)	
Asian	0 (0.00)	1 (1.0)	4 (1.9)	2 (0.9)	
Hispanic	11 (10.1)	9 (9.1)	19 (9.0)	25 (11.8)	
Other	2 (1.8)	2 (2.0)	7 (3.3)	4 (1.9)	

[1] P-value for age based on ANOVA for per protocol groups. P-values for sex and race based on Mantel-Hanszel test for pre protocol groups.

Days on Therapy

	Number of Patients			
Days of Therapy	Levofloxacin		Vehicle	
	Per Protocol/Intent to Treat		Per Protocol/Intent to Treat	
2	0	1	0	3
3	0	7	1	5
4	2	5	3	5
5	91	161	80	152 -
6	6	12	11	31
7	5	16	4	6
8	1	4	0	3
9	0	0	0	1

Disposition by Investigator

Site	Investigator	0.5% Levofloxacin	0.3% Ofloxacin
3	Abelson	12	11
5	Schwab	7	6
6	O'Brien	0	0
9	Wapner	22	24
11	Mundorf	2	2
25	Dell	18	18
26	Braunstein	5	5
27	Caine	14	14
29	Cavanaugh	6	6
32	Donshik	0	0
34	Friedlaender	10	8
37	Levy	14	14
38	McCulley	12	12
39	Milstein	7	7
40	Moran	18	18
41	Prepas	0	1
43	Reidy	13	14
44	Robin	0	1
45	Sall	2	3
47	Sugar	7	7
49	Valluri	10	11
50	Wolf	5	5
56	Bahadur	10	8
61	Lichtenstein	17	17

APPEARS THIS WAY
ON ORIGINAL

Discontinued Patients

Site	Patient	Group	Baseline Culture	Reason
3	1020	0.5% LVFX	Negative	ADR- Increased lid swelling
38	1907	0.5% LVFX	Negative	ADR- Discomfort upon instillation
9	3128	0.5% LVFX	Negative	Lost to follow-up
25	1530	0.5% LVFX	Negative	Lost to follow-up
27	1308	0.5% LVFX	Negative	Lost to follow-up
43	2503	0.5% LVFX	Negative	Lost to follow-up
43	2504	0.5% LVFX	Negative	Lost to follow-up
56	1112	0.5% LVFX	Negative	Lost to follow-up
43	2505	0.5% LVFX	Negative	Negative baseline culture
50	3207	0.5% LVFX	Negative	Patient decision
39	2009	0.5% LVFX	Positive	Clinical worsening
9	3123	0.5% LVFX	Positive	Lost to follow-up
38	1904	0.5% LVFX	Positive	Non-compliance
27	1314	0.5% LVFX	Positive	Protocol violation – steroidal inhaler
9	3127	0.3% OFLX	Negative	ADR- Allergic reaction
3	1018	0.3% OFLX	Negative	Clinical worsening
27	1302	0.3% OFLX	Negative	Clinical worsening
26	1204	0.3% OFLX	Negative	Clinical worsening
27	1319	0.3% OFLX	Negative	Clinical worsening
39	2012	0.3% OFLX	Negative	Lost to follow-up
40	2135	0.3% OFLX	Negative	Lost to follow-up
43	2502	0.3% OFLX	Negative	Lost to follow-up
43	2512	0.3% OFLX	Negative	Lost to follow-up
56	1106	0.3% OFLX	Negative	Negative baseline culture
43	2508	0.3% OFLX	Negative	Negative baseline culture
27	1311	0.3% OFLX	Positive	Clinical worsening
27	1323	0.3% OFLX	Positive	Clinical worsening
49	3018	0.3% OFLX	Positive	Clinical worsening
37	1820	0.3% OFLX	Positive	Lost to follow-up
43	2501	0.3% OFLX	Positive	Non-compliance
47	2907	0.3% OFLX	Positive	Non-compliance
37	1812	0.3% OFLX	Positive	Patient decision
38	1924	0.3% OFLX	Positive	Patient decision
43	2511	0.3% OFLX	Positive	Patient decision
39	2007	0.3% OFLX	Positive	PI decision

APPEARS THIS WAY
ON ORIGINAL

8.1.1.4.2 Efficacy endpoint outcomes

Summary of Clinical Cure and Microbial Eradication by Study Period

Study Period Per-Protocol	Outcome	0.5% LVFX	0.3% OFLX	Confidence Interval	p-value
Interim (Day 3-5)	Clinical Cure	25% (27/106)	26% (24/94)	-8 to 7%	0.969
	Microbial Eradication	84% (89/106)	86% (81/94)		0.435
Final (Day 6-10)	Clinical Cure	79% (81/103)	81% (75/93)	-11% to 8%	0.778
	Microbial Eradication	89% (92/103)	80% (74/92)		**0.034***
Study Period Intent to Treat	Outcome	0.5% LVFX	0.3% OFLX		p-value
Interim (Day 3-5)	Clinical Cure	25% (50/203)	24% (47/195)		0.626
Final (Day 6-10)	Clinical Cure	77% (148/192)	74% (142/192)		0.517

* $p<0.05$. Favors 0.5% LVFX

APPEARS THIS WAY
ON ORIGINAL

Eradication Rates from Baseline to Final by Organism

Organism	0.5% LVFX	0.3% OFLX
[redacted]		
Moraxella catarrhalis	100% (1/1)	-
Enterobacter/Pantoea	100% (1/1)	-
Escherichia coli	100% (1/1)	-
Proteus mirabilis	100% (2/2)	-
Serratia marcescens	100% (3/3)	100% (1/1)
Other Neisseria	100% (1/1)	100% (1/1)
Acinetobacter	83% (5/6)	75% (3/4)
Haemophilus influenzae	92% (37/40)	89% (32/36)
Haemophilus parainfluenzae	100% (1/1)	100% (1/1)
Pseudomonas aeruginosa	-	0% (0/1)
Other Pseudomonas/Other Non-Enterobacteriaceae	100% (4/4)	100% (2/2)
[redacted]		
Staphylococcus aureus	100% (13/13)	100% (19/19)
Staphylococcus epidermidis	100% (18/18)	100% (15/15)
Other coagulase negative Staphylococcus	100% (3/3)	100% (2/2)
Streptococcus, Group A, beta hemolytic (S. pyogenes)	100% (1/1)	-
Streptococcus pneumoniae	86% (24/28)	68% (17/25)
Other Streptococcus (Groups D, G; non-grouped; viridans)	100% (9/9)	100% (5/5)
Micrococcus/Stomatococcus	100% (4/4)	100% (1/1)
Corynebacterium	100% (2/2)	100% (2/2)

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

BEST POSSIBLE COPY

8.1.1.4.3 Safety outcomes

Adverse Experience	0.5% Levofloxacin (n=207)	0.3% Ofloxacin (n=206)
Conjunctivitis	15 (7%)	17 (8%)
Headache	7	6
Decreased vision	5	2
Eye pain	5	2
Ocular burning	4	3
Cyst	3	5
Foreign body sensation	3	1
Photophobia	2	2
Lid Edema	2	1
Pharyngitis	2	1
Ocular discomfort	2	0
Subconjunctival hemorrhage	2	0
Ocular itching	1	3
Rash	1	2
Rhinitis	1	2
Diarrhea	1	1
Dry Eye	1	1
Tearing	1	1
Bronchitis	1	0
Conjunctival discharge	1	0
Conjunctival follicles	1	0
Corneal infiltrate	1	0
Cough Increase	1	0
Epistaxis	1	0
Joint Disease	1	0
Lid Erythema	1	0
Ocular edema	1	0
Otitis	1	0
Palpitation	1	0
Sinusitis	1	0
Tooth pain	1	0
Allergic reaction	0	2
Hyperemia	0	2
Infection	0	2
Pain	0	2
Abnormal accommodation	0	1
Conjunctival staining	0	1
Edema	0	1
Fever	0	1
Herpes Zoster	0	1
Lid Pain	0	1
Nausea	0	1
Tinnitus	0	1

8.1.1.5 Reviewer's Conclusions Regarding Efficacy Data

Levofloxacin appears to be equivalent to ofloxacin with respect to clinical and microbiological efficacy. The clinical cure rate for each group is approximately 80%. Efficacy was demonstrated primarily against Haemophilus influenzae, Streptococcus pneumonia, Staphylococcus epidermidis, and Staphylococcus aureus.

8.1.2 Reviewer's Trial # 2 Sponsor's protocol # 03-004

8.1.2.1 Objective/Rationale

The objective of this study was to evaluate the clinical and microbial efficacies, and safety of 0.5% levofloxacin ophthalmic solution (0.5% LVFX) compared to placebo for the treatment of bacterial conjunctivitis in adults and children 2 years of age and older.

8.1.2.2 Design

Multicenter, randomized, placebo-controlled, double-masked comparison of 0.5% LVFX versus its vehicle in patients with bacterial conjunctivitis.

8.1.2.3 Protocol *-same as Study #1*

Investigators

Casey, R	King-Drew Medical Center, 1202 S. Wilmington Ave., Room 5009, Los Angeles, CA 90059 4560 Admiralty Way, Suite 354, Marina Del Rey, CA 90292 University of California, Los Angeles, Jules Stein Eye Institute, 100 Stein Plaza 3-217, Los Angeles, CA 90024
Cerise, D	4324 Veterans Blvd., Metarie, LA 70006
Crabb, L	Eye Tech, 5496 Knight Arnold Rd., Memphis, TN 38115
Forstot, S	8381 Southpark Lane, Littleton, CO 80120
Foulks, G	University of Pittsburgh, Department of Ophthalmology, 203 Lothrop Street, Room 817, Pittsburgh, PA 15213
Hwang, D	University of California, San Francisco, 10 Kirkham Street, K-301 Box 0730 San Francisco, CA 94143-0730
Kretchman, G	1010 E. McDowell #406, Phoenix, AZ 85006 10585 N. Tatum Blvd., St. #D131, Paradise Valley, AZ 85253 2337 W. Northern, Phoenix, AZ 85021
Montgomery, J	Texan Eye Care, 1700 S. Mopac, Austin, TX 78746 Texan Eye Care, 1020 W. 34th Street, Austin, TX 78705
Raizman, M	New England Medical Center, 750 Washington Street, Boston, MA 02111
Rotberg, M	Charlotte Eye, Ear, Nose and Throat Associates, PA, 1600 E. Third Street, Charlotte, NC 28204 Park Crossing Medical Center, 10352 Park Road, Charlotte, NC 28210 101 W.T. Harris Blvd., Suite 5103, Charlotte, NC 28260 1450 Matthews Township Parkway, Suite 110, Matthews, NC 28105 701 East Roosevelt Blvd., Monroe, NC 28112 209 Park Street, Suite 600, Belmont, NC 28012
Rubin, J	999 E. Basse Road, #128B, San Antonio, TX 78209
Schanzlin, D	Shiley Eye Center, University of California, San Diego, 9500 Gilman Drive, Dept. 0946, La Jolla, CA 92093-0946
Shulman, D	999 E. Basse Road, #116, San Antonio, TX 78209
Terry, M	Devers Eye Institute, 1040 NW 22nd Avenue, Suite 200, Portland, OR 97210-3065
Zloty, P	Eye Institute of the South, 2800 Ross Clark Circle, SW, Dothan, AL 36301

Reviewer's Comments: *The financial disclosure forms have been reviewed.*

8.1.2.3.1 Population

A sufficient number of patients were be enrolled to obtain approximately 100 culture positive patients, including children 2 years of age and older, meeting all eligibility requirements and exhibiting ocular discharge and redness.

8.1.2.3.2 Endpoints

Primary Clinical Efficacy *-same as Study #1*

Primary Microbial Efficacy *-same as Study #1*

8.1.2.4 Results

8.1.2.4.1 Populations enrolled/analyzed

Summary of Demographics

	Per Protocol		All Patients		
	0.5% LVFX	Vehicle	0.5% LVFX	Vehicle	P-VALUE[1]
Number of Patients:	60	57	121	118	
AGE					0.9591
MEAN(SD)	31.4 (22.3)	31.6 (23.0)	34.6 (20.2)	33.7 (21.1)	
MEDIAN	29	29			
MIN-MAX	2-91	2-76	2-91	2-86	
>16 years	41 (68%)	37 (65%)			
12-16 years	3 (5%)	3 (5%)			
2-11 years	16 (27%)	17 (30%)			
SEX: N(%)					0.0355
Female	38 (63%)	25 (44%)	77 (64%)	60 (51%)	
Male	22 (37%)	32 (56%)	44 (36%)	58 (49%)	
RACE: N(%)					0.6540
Caucasian	44 (73%)	46 (81%)	91 (75%)	92 (78%)	
Black	10 (17%)	11 (10%)	12 (10%)	18 (15%)	
Asian	0 (0.00)	1 (2%)	1 (1%)	1 (1%)	
Hispanic	5 (8%)	3 (5%)	15 (12%)	6 (5%)	
Other	1 (2%)	1 (2%)	2 (2%)	1 (1%)	

[1] P-value for age based on ANOVA for per protocol groups. P-values for sex and race based on Mantel-Hanszel test for pre protocol groups.

Disposition by Investigator

Site	Investigator	Enrolled/Culture Positive	
		0.5% Levofloxacin	Vehicle
1	Rubin	2/2	2/1
8	Shulman	16/5	17/8
28	Casey	1/1	0/0
30	Cerise	18/9	17/7
31	Crabb	12/8	13/6
33	Foulks	2/0	0/0
35	Hwang	3/0	2/1
36	Kretchman	18/9	18/10
42	Raizman	1/1	1/1
46	Schanzlin	6/3	7/1
48	Terry	7/4	7/3
57	Forstot	0/0	0/0
58	Zloty	2/1	1/0
59	Rotberg	25/18	25/16
62	Montgomery	13/9	13/11
Total		126/70	123/65

Days on Therapy

	Number of Patient			
Days of Therapy	Levofloxacin		Vehicle	
	Per Protocol	Intent to Treat	Per Protocol	Intent to Treat
2	0	1		2
3	0	4	1	4
4	0	0	0	0
5	50	102	47	95
6	6	10	8	14
7	2	2	0	2
8	1	1	1	2
13	1	1	0	0

Discontinued Patients

Site	Patient	Group	Baseline Culture	Reason
8	5816	Levofloxacin	Negative	ADR-Corneal infiltrate
30	5110	Levofloxacin	Negative	ADR-Allergic reaction
36	5423	Levofloxacin	Negative	ADR-Worsening of conjunctival symptoms
58	6101	Levofloxacin	Negative	ADR-Diarrhea
31	5524	Levofloxacin	Negative	Clinical Worsening
31	5520	Levofloxacin	Negative	Lost to follow-up
31	5514	Levofloxacin	Positive	Lost to follow-up
1	6402	Levofloxacin	Positive	Non-compliance
31	5502	Levofloxacin	Positive	Non-compliance
59	6030	Levofloxacin	Positive	Non-compliance
36	5403	Levofloxacin	Positive	Patient has only 1 seeing eye
1	6401	Vehicle	Negative	ADR-Subepithelial infiltrate
8	5827	Vehicle	Negative	ADR-Corneal infiltrate
31	5513	Vehicle	Negative	Clinical worsening
31	5517	Vehicle	Negative	Lost to follow-up
48	5903	Vehicle	Negative	Lost to follow-up
48	5912	Vehicle	Negative	Lost to follow-up
42	5602	Vehicle	Positive	ADR-Pneumonia
59	6206	Vehicle	Positive	Clinical worsening
62	6309	Vehicle	Positive	Lost to follow-up
59	6224	Vehicle	Positive	Non-compliance
36	5402	Vehicle	Positive	Uncooperative

8.1.2.4.2 Efficacy endpoint outcomes

Summary of Clinical Cure and Microbial Eradication by Study Period

Study Period Per-Protocol	Outcome	0.5% LVFX	Vehicle	Confidence Interval	p-value
Interim (Day 3-5)	Clinical Cure	27% (16/59)	24% (13/55)	-11% to 19%	0.642
	Microbial Eradication	95% (56/59)	49% (27/55)		**<0.001**
Final (Day 6-10)	Clinical Cure	78% (46/59)	61% (34/56)	9% to 37%	**0.020**
	Microbial Eradication	92% (54/59)	53% (29/55)		**<0.001**
Study Period Intent to Treat	Outcome	0.5% LVFX	Vehicle		p-value
Interim (Day 3-5)	Clinical Cure	25% (30/119)	19% (21/112)		0.144
Final (Day 6-10)	Clinical Cure	72% (82/114)	65% (58/113)		0.195

* $p<0.05$. Favors 0.5% LVFX

Eradication Rates from Baseline to Final by Organism

Organism	0.5% LVFX	Vehicle
[redacted]		
Moraxella catarrhalis	-	100% (1/1)
Enterobacter/Pantoea	-	100% (1/1)
Escherichia coli	-	-
Proteus mirabilis	100% (1/1)	100% (1/1)
Serratia marcescens	100% (1/1)	100% (1/1)
Other Neisseria	-	-
Acinetobacter	100% (1/1)	100% (3/3)
Haemophilus influenzae	92% (12/13)	52% (12/23)
Haemophilus parainfluenzae	100% (2/2)	-
Pseudomonas aeruginosa	-	-
Other Pseudomonas/Other Non-Enterobacteriaceae	100% (2/2)	
[redacted]		
Staphylococcus aureus	100% (11/11)	83% (5/6)
Staphylococcus epidermidis	100% (4/4)	100% (7/7)
Other coagulase negative Staphylococcus	-	100% (2/2)
Streptococcus, Group A, beta hemolytic (S. pyogenes)	-	-
Streptococcus pneumoniae	84% (21/25)	47% (9/19)
Other Streptococcus (Groups D, G; non-grouped; viridans)	100% (6/6)	100% (4/4)
Micrococcus/Stomatococcus	-	100% (1/1)
Corynebacterium	100% (3/3)	-

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

BEST POSSIBLE COPY

8.1.2.4.3 Safety outcomes

Adverse Experience	0.5% Levofloxacin (n=124)	Vehicle (n=120)
Conjunctivitis	18 (15%)	12 (10%)
Headache	7	2
Decreased vision	4	3
Infection	3	2
Ocular burning	3	0
Pharyngitis	3	0
Pain	2	1
Corneal staining	2	0
Ear pain	2	0
Corneal infiltrate	1	1
Keratitis	1	1
Nausea	1	1
Ocular itching	1	1
Photophobia	1	1
Allergic reaction	1	0
Browache	1	0
Diarrhea	1	0
Dry Eye	1	0
Fever	1	0
Ocular edema	1	0
Rhinitis	1	0
Sinusitis	1	0
Tachycardia	1	0
Epitheliopathy	0	3
Ocular discomfort	0	3
Abdominal pain	0	1
Lid margin discharge	0	1
Lymphadenopathy	0	1
Pneumonia	0	1
Tooth pain	0	1

8.1.2.5 Reviewer's Conclusions Regarding Efficacy Data

Levofloxacin was superior to its vehicle with respect to clinical and microbiological efficacy. The clinical cure rate for the levofloxacin group was approximately 80%. Efficacy was demonstrated primarily against Haemophilus influenzae, Streptococcus pneumonia, and Staphylococcus aureus.

8.1.3 Reviewer's Study #3 Protocol 03-002

Title: **Phase II pilot clinical and microbial evaluation of 0.5% levofloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis and/or blepharoconjunctivitis**

Design

Multicenter, randomized, active-controlled, double-masked comparison of 0.5% LVFX versus 0.3% OFLX in patients with bacterial conjunctivitis. A sufficient number of patients were to be enrolled to obtain approximately 30 culture-positive patients, including approximately 10 children.

Enrolled patients dosed with masked study medication for 5 days. Patients instilled one to two drops in the infected eye(s) every 2 hours, up to 8x/day, while awake on Days 1 and 2, then one to two drops every 4 hours, up to 4x/day, while awake on Days 3 through 5. The patients were examined at Visit 1 (Day 1), Visit 2 (Day 3+1), and Visit 3 (Day 7±1).

Summary of Demographics

	TREATMENT	
	0.5% LVFX	0.3% OFLX
Number of Patients:	15	17
Age		
Mean(SD)	26.40 (17.14)	44.12 (25.33)
Min-Max	2-70	5-91
>16 years	10 (67.00)	15 (88.00)
12-16 years	3 (20.00)	0 (0.00)
2-11 years	2 (13.00)	2 (12.00)
Gender: N(%)		
Female	13 (86.67)	14 (82.35)
Male	2 (13.33)	3 (17.65)
RACE: N(%)		
Caucasian	10 (67.00)	16 (94.00)
Non-Caucasian	5 (33.00)	1 (6.00)
POPULATION		
Blepharoconjunctivitis	0 (0.00)	1 (6.00)
Bacterial Conjunctivitis	15 (100.00)	16 (94.00)

Primary Efficacy Variables

Clinical Cure	Levofloxacin	Ofloxacin
Visit 2	20%	18%
Visit 3	100%	76%
Microbial Eradication		
Visit 2	53%	35%
Visit 3	80%	65%

Organism Isolated

	Number of Patients Levofloxacin		Number of Patients Ofloxacin	
[redacted]				
Streptococcus pneumoniae	3	0	2	1
Serratia marcescens	1	0		
Acinetobacter	2	0		
Hemophilus influenzae	1	1	3	1
Staphylococcus aureus	2	1	2	0
Other Streptococcus (Groups D, G: non-group)				
Staphylococcus epidermidis	4	3	4	2
Other coagulase (-) Staphylococcus	7	2	10	4
Micrococcus	3	3	2	2
Bacilius	1	1	2	2
Corynebacterium	1	0	3	0

Safety Results *Consistent with previous studies.*

Reviewer's Summary Comments: ***The study is consistent with Protocols 03-003 and 03-004, except that this study has a smaller number of subjects.***

BEST POSSIBLE COPY

Japanese Studies:

The Japanese clinical trial system collects data in a unique ranking fashion. The three major endpoints are efficacy, safety, and usefulness. Results of these studies are summarized using the ranking system.

Clinical Assessment

2 points	Markedly effective	Disappearance of detected bacteria (suspected causative bacteria) within 4 days, and withdrawal of major clinical sign within 1 week
1 point	Effective	Bacteria disappear within 1 week, and major clinical sign disappears within 2 weeks, or Bacteria disappear within 4 days, and symptom scores are ½ or less within 1 week, or Symptom score are 1/3 or less within 1 week even if bacteria do not disappear
0 point	Not effective	No effectiveness is seen
-1 point	Aggravated	Major symptoms or signs have worsened from the first visit

Overall Safety

2 points	-	No adverse event observed
1 point	+	Mild adverse event is present but the administration of the study drug was continued
0 point	++	Adverse event is present and the study drug administration had to be discontinued
-1 point	+++	Adverse event is present and treatment for the adverse event is required

Usefulness (Total Score for Clinical Efficacy and Safety)

4 points	Extremely useful
3 points	Very useful
1 point for efficacy and 1 point for safety	Slightly useful
0 points for efficacy and safety	Not useful
-1 points for either efficacy or safety	Harmful

Reference 97002. Usui M. Clinical evaluation of levofloxacin ophthalmic solution – A multicenter phase II double-masked clinical trial. J Eye. 1997; 14(2):299-307.

Double-masked, active-controlled, multicenter Phase II dose-response clinical trial was conducted to evaluate the efficacy and safety of two concentrations of levofloxacin ophthalmic solution (LVFX), 0.3% and 0.5%, to determine the optimal concentration of LVFX, and to compare the safety and efficacy of 0.3% and 0.5% LVFX to 0.3% ofloxacin ophthalmic solution (OFLX) in 252 patients with external ocular infections.

This study was conducted by 33 investigators at 33 centers in Japan from December 1993 to September 1994. Patients with external ocular infections (e.g., conjunctivitis, blepharitis, hordeolum, tarsitis, dacrocystitis, keratitis, corneal ulcer) were randomly assigned to receive either 0.3% LVFX, 0.5% LVFX or 0.3% OFLX. Patients administered one drop 3x daily in the infected eye(s) for up to 2 weeks.

Patients were seen for a total of 4 visits: baseline, after 3(+1)-days, 7-days and 14-days of treatment. At each visit, clinical signs and symptoms and other related symptoms were rated for severity using a 3-point scale (-:absent, +: present, ++: marked). Bacterial cultures were also collected at each visit.

Patient Demographics

Study drug		0.5% LVFX	0.3% LVFX	0.3% OFLX	p-value
No. of evaluable cases		64	65	53	
Gender	Male	26	30	17	0.3102
	Female	38	35	36	0.2982
Age group	≤ 9	3	3	1	
	10 – 19	1	1	1	
	20 – 29	7	11	6	
	30 – 39	6	11	7	
	40 – 49	6	2	5	0.7972
	50 – 59	12	9	8	
	60 – 69	14	9	8	
	70 – 79	11	12	11	
	≥80	4	7	6	
	Mean±S.D.	54 ±21	51 ±24	55 ±22	0.5041
Diagnosis					
Conjunctivitis		41	45	39	
Blepharitis		3	2	3	
Hordeolum		8	6	3	0.7877
Tarsitis		4	9	7	
Dacryocystitis		7	3	2	
Keratitis		2	1	1	
Corneal ulcer		1	2	1	

Results

	0.5% LVFX	0.3% LVFX	0.3% OFLX
Markedly Effective	67%	50%	57%
Effective	25%	41%	34%

Reference 97051. Usui M. Effect of levofloxacin ophthalmic solution on preoperative sterilization. J Eye. 1997; 14(6):953-956.

Open-label, multicenter study was conducted to evaluate the anti-microbial efficacy of preoperative treatment with 0.5% levofloxacin (LVFX) topical ophthalmic solution before ocular surgery. This study was conducted by 10 investigators at four institutions in Japan from June 1995 to May 1996. A total of 75 male and female patients were enrolled into the study. 0.5% LVFX was administered one drop 5x daily for 2 days, starting the 2 days prior to surgery. After instillation, an antiseptic gauze dressing (or eye patch) was applied. The antiseptic gauze dressing (or eye patch) was changed after each instillation, and the eyes were kept covered by the antiseptic gauze dressing (or eye patch) until immediately prior to surgery. Eye patches were worn at bedtime on the day before surgery. Bacterial specimens were collected from the conjunctival sac 2 days before surgery before dosing with 0.5% LVFX and on the morning of surgery after the last dose.

Results

Seventy-five patients participated in this study. Twenty-five patients were excluded from efficacy analysis due to negative baseline culture results, dosing violations, or removal of antiseptic gauze dressing (or eye patch). One patient, who dropped out of the study due to itching induced by the tape used on the antiseptic gauze dressing, was excluded from safety evaluation.

In 50 cases evaluated for efficacy, 35 were confirmed to be sterilized for a efficacy rate of 70.0%. For most aerobic bacteria including *Staphylococcus epidermidis* and *Corynebacterium* sp. and an anaerobic bacterium such as *Propionibacterium acnes*, 0.5% LVFX achieved an efficacy rate of 60% or greater.

Reference 97070. Usui M. Clinical Evaluation of Levofloxacin Ophthalmic Solution – Phase III Open-Label Trial. J Eye. 1997; 14(7):1113-1118.

Open-label, multicenter clinical trial was conducted to evaluate the efficacy and safety of 0.5% LVFX in patients with external ocular infections (e.g., conjunctivitis, blepharitis, hordeolum, tarsitis, dacrocystitis, keratitis or corneal ulcer). This study was conducted by 33 investigators at 16 institutions in Japan from July 1995 to May 1996. One hundred and fifty-two male and female patients were enrolled into the study. Patients were given one drop of 0.5% LVFX 3x daily in the infected eye(s) for up to 2 weeks.

Patients were seen for a total of four visits, baseline, and after 3 (+1), 7 and 14 days of treatment. At each visit, clinical signs and symptoms and other related symptoms were evaluated. The severity of clinical signs and symptoms were rated on a 3-point scale, (–: absent, +: present, ++: markedly present). Very severe symptoms were classified (+++), and very mild symptoms were classified (±).

Patient demographics

Total number of evaluated cases		115
Gender	Male	50
	Female	65
Age	0-9	3
	10-19	2
	20-29	17
	30-39	12
	40-49	7
	50-59	10
	60-69	27
	70-79	22
	80-	15
Total number of evaluated cases		115
Diagnosis (Multiple diagnosis in one patient)	Conjunctivitis	68
	Blepharitis	5
	Hordeolum	8
	Tarsitis	10
	Dacryocystitis	13
	Keratitis	18
	Corneal ulcer	3

Results

Markedly effective = 56% (64/115)
Effective = 29% (33/115)

Reference 97031. Usui M. Clinical evaluation of levofloxacin ophthalmic solution – a multicenter Phase III double-masked clinical trial. J Eye. 1997; 14(4):641-648

Double masked, multicenter, active-controlled, parallel-group Phase III trial was conducted to compare the efficacy and safety of 0.5% LVFX vs. 0.3% OFLX in patients with external ocular infections. Patients with external ocular infections being diagnosed as having conjunctivitis, blepharitis, hordeolum, tarsitis, dacryocystitis, keratitis, or corneal ulcer were included in the study. This study was conducted by 77 investigators at 45 institutions in Japan from April 1995 to March 1996. A total of 366 male and female patients were enrolled into the study and were randomized to receive either 0.5% LVFX or 0.3% OFLX (180 in the LVFX group and 186 in the OFLX group). Patients administered one drop of study medication three times daily for up to 2 weeks. Patients were seen for a total of four visits, baseline, and after 3 (+1), 7 and 14 days of treatment (3-7-14 method). At each visit, clinical signs and symptoms were rated for severity with a 3-point scale. Bacterial cultures were collected at baseline and after 3 (+1) days and 7 days of treatment.

Of the 366 patients enrolled into the study, 73 patients with negative culture results, protocol violations, or who were discontinued (33 LVFX, 40 OFLX) were excluded from the efficacy evaluation. Of the 293 evaluable patients, 287 were evaluated for clinical efficacy. Six patients (3 LVFX, 3 OFLX) were excluded due to protocol violations or discontinuation. The clinical efficacy rate (judged "Effective" or better) was 97.2% (140/144) and 88.1% (126/143) in the LVFX and OFLX groups, respectively.

APPEARS THIS WAY ON ORIGINAL

Anti-infective Susceptibilities

Organism Gram-negative Isolates	% Susceptible (susceptible / tested) LVFX DD	LVFX MIC	LVFX MIC_{90} (µg/ml)	CPFX DD	CPFX MIC	CPFX MIC_{90} (µg/ml)	OFLX DD	OFLX MIC	OFLX MIC_{90} (µg/ml)	No. of Isolates
Acinetobacter sp. (Total)	100 (18/18)	NT	NT	100 (18/18)	NT	NT	100 (18/18)	NT	NT	7
A. baumannii	100 (4/4)	NT	NT	100 (4/4)	NT	NT	100 (4/4)	NT	NT	4
A. calcoaceticus	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
A. junii	100 (2/2)	NT	NT	100 (2/2)	NT	NT	100 (2/2)	NT	NT	2
A. lwoffii	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
A.caviae	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
A. hydrophila	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
Alcaligenes xylosoxidans	100 (2/2)	NT	NT	100 (2/2)	NT	NT	100 (2/2)	NT	NT	2
Brevundimonas vesicularis	0 (0/1)	0 (0/1)	8	0 (0/1)	0 (0/1)	8	0 (0/1)	0 (0/1)	16	1
Chryseomonas luteola	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
Citrobacter freundii	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
E. aerogenes	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
E. agglomerans	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
E. cloacae	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
Escherichia coli	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
Flavimonas oryzihabitans	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
Flavobacterium gleum	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
H. influenzae	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
H. parainfluenzae	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
K. oxytoca	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
K. pneumoniae	100 (3/3)	100 (3/3)	2	67 (2/3)	67 (2/3)	8	67 (2/3)	67 (2/3)	4	3
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
M. catarrhalis	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
M. osloensis	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
N. mucosa	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
N. sicca	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
N. subflava	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
Ochrobactrum anthropi	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

Organism Gram-negative Isolates	% Susceptible (susceptible / tested)									
	LVFX			CPFX			OFLX			
	DD	MIC	MIC_{90} (µg/ml)	DD	MIC	MIC_{90} (µg/ml)	DD	MIC	MIC_{90} (µg/ml)	No. of Isolates
Pantoea agglomerans	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
Proteus mirabilis	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
P. aeruginosa	100 (3/3)	100 (3/3)	0.5	100 (3/3)	100 (3/3)	0.12	100 (3/3)	100 (3/3)	1	3
P. cepacia	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
P. diminuta	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
P. fluorescens	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
P. paucimobilis	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
P. putida	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
P. stutzeri	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
P. vesicularis	100 (2/2)	NT	NT	50 (1/2)	NT	NT	50 (1/2)	NT	NT	2
Serratia marcescens	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
Sphingomonas paucimobilis	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
Stenotrophomonas maltophilia	100 (3/3)	100 (3/3)	2	33 (1/3)	33 (1/3)	4	100 (3/3)	67 (2/3)	4	3
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
C. pseudodiphtheriticum	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
C aquaticum	100 (1/1)	NT	NT	0 (0/1)	NT	NT	0 (0/1)	NT	NT	1
C. group ANF	100 (1/1)	NT	NT	0 (0/1)	NT	NT	100 (1/1)	NT	NT	1
C. group F	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
C. group G-1	100 (4/4)	NT	NT	100 (4/4)	NT	NT	100 (4/4)	NT	NT	4
C. xerosis	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
Enterococcus faecalis	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
M. luteus	100 (4/4)	NT	NT	75 (3/4)	NT	NT	75 (3/4)	NT	NT	4
M. lylae	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
M. varians	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
S. aureus	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
S. capitis	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
S. epidermidis	90 (18/20)	90 (18/20)	0.25	85 (17/20)	90 (18/20)	1	90 (18/20)	90 (18/20)	0.5	20
S. haemolyticus	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

Organism Gram-negative Isolates	% Susceptible (susceptible / tested)									
	LVFX			CPFX			OFLX			
	DD	MIC	MIC_{90} (µg/ml)	DD	MIC	MIC_{90} (µg/ml)	DD	MIC	MIC_{90} (µg/ml)	No. of Isolates
S. hominis	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
S. simulans	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
S. warneri	100 (1/1)	NT	NT	100 (1/1)	NT	NT	100 (1/1)	NT	NT	1
Stomatococcus mucilaginosus	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
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
S. adjacens	100 (1/1)	100 (1/1)	1	0 (01/1)	100 (1/1)	2	0 (0/1)	100 (1/1)	2	1
S. agalactiae	100 (1/1)	100 (1/1)	1	0 (01/1)	100 (1/1)	1	100 (1/1)	100 (1/1)	2	1
S. anginosus	100 (1/1)	100 (1/1)	1	100 (1/1)	100 (1/1)	1	100 (1/1)	100 (1/1)	2	1
S. bovis	100 (1/1)	100 (1/1)	1	0 (01/1)	0 (01/1)	2	0 (0/1)	100 (1/1)	2	1
S. constellatus	100 (1/1)	100 (1/1)	0.5	100 (1/1)	100 (1/1)	0.5	100 (1/1)	100 (1/1)	1	1
S. gordonii	100 (2/2)	100 (2/2)	0.5	100 (2/2)	100 (2/2)	0.5	100 (2/2)	100 (2/2)	1	2
S. intermedius	100 (3/3)	100 (3/3)	2	33 (1/3)	33 (1/3)	8	33 (1/3)	33 (1/3)	4	3
S. mitis	100 (14/14)	100 (14/14)	2	21 (3/14)	50 (7/14)	4	50 (7/14)	71 (10/14)	4	14
S. oralis	100 (11/11)	100 (11/11)	2	18 (2/11)	36 (4/11)	4	36 (4/11)	91 (10/11)	2	11
S. pneumoniae	100 (19/19)	100 (19/19)	1	58 (11/19)	95 (18/19)	1	89 (17/19)	100 (19/19)	2	19
S. pyogenes	100 (1/1)	100 (1/1)	0.5	0 (0/1)	100 (1/1)	0.25	100 (1/1)	100 (1/1)	1	1
S. salivarius	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

*No growth for 2 isolates DD = Disk Diffusion test MIC = Broth Dilution test

Reviewer's Comments: *Organisms for the in-vitro susceptibility list in the package insert will be based on the microbiology review.*

APPEARS THIS WAY
ON ORIGINAL

9. Overview of Efficacy

Reviewer's Comments: *Efficacy has been established in two adequate and well controlled studies in which the clinical cure for susceptible microorganisms was approximately 79%. The third study (pilot) study was under powered and therefore not expected to demonstrate efficacy. The specific microbial organisms are listed below for studies 1-3.*

Microbial Eradication Rates by Final Organism –Studies 1, 2, & 3

Organism	0.5% Lvfx	0.3% Oflx	Vehicle
Enterobacter/Pantoea	1/1		1/1
Escherichia coli	*1/1*		
Proteus mirabilis	*3/3*		*1/1*
Serratia marcescens	*5/5*	*1/1*	*1/1*
Haemophilus influenzae	*49/54*	*34/38*	*12/23*
Haemophilus parainfluenzae	*3/3*	*1/1*	
Other Neisseria	1/1	1/1	
Moraxella	1/1		
Acinetobacter	8/9	3/ 4	3/3
Pseudomonas aeruginosa		*0/1*	
Other Pseudomonas/Other Enterobacteriaceae	6/6	2/2	
Corynebacterium	5/5	5/5	
Staphylococcus aureus	*25/26*	*21/21*	*5/6*
Staphylococcus epidermidis	*23/26*	*17/19*	*7/7*
Other coag neg staph	8/10	8/12	2/2
Micrococcus/Stomatococcus	4/7	1/3	1/1
Streptococcus, Group A, Beta hemolytic	1/1		
Streptococcus pneumoniae	*48/56*	*18/26*	*9/19*
Other Strept(Group D,G,Non-grouped, viridans)	15/15	6/6	4/4
Bacillus	0/1		

Reviewer's Comments: *The criteria used to identify susceptible microorganisms for this product and previous ophthalmic drug products has been to identify speciated microorganisms in which at least 5 patients have been treated with the test agent and in which at least 80% of the cases were microbiologically cured.*

APPEARS THIS WAY
ON ORIGINAL

10.1 Significant/Potentially Significant Events

10.1 Deaths

Subject 5602 (Study 03-004) experienced pneumonia which required hospitalization. There were no deaths in the study population.

10.2.1 ADR Incidence Tables

All Ocular Adverse Events in Bacterial Conjunctivitis Patient Population Regardless of Relationship: By Frequency

Event	0.5% LVFX (n=353)	0.3% OFLX (n=228)	Placebo (n=120)
	N(%)	N(%)	N(%)
Decreased vision	9 (2.5)	2(0.9)	3(2.5)
Ocular burning	7 (2.0)	3(1.3)	
Ocular pain	5 (1.4)	2(0.9)	
Foreign body sensation	3 (0.8)	1(0.4)	
Photophobia	3 (0.8)	2(0.9)	1(0.8)
Ocular discomfort	2 (0.6)		3(2.5)
Ocular dryness	2 (0.6)	1(0.4)	
Lid edema	2 (0.6)	1(0.4)	
Subconjunctival hemorrhage	2 (0.6)		
Corneal infiltrate	2 (0.6)		1(0.8)
Ocular itching	2 (0.6)	3(1.3)	1(0.8)
Corneal staining	2 (0.6)		
Allergic reaction	1 (0.3)*	2(0.9)	
Browache	1 (0.3)		
Chalazion	1 (0.3)		
Conjunctival discharge	1 (0.3)		
Ocular edema	1 (0.3)		
Lid erythema	1 (0.3)		
Conjuncival follicles	1 (0.3)		
Keratitis	1 (0.3)		1(0.8)
Tearing	1 (0.3)	1(0.4)	
Abnormal accommodation		1(0.4)	
Conjunctival abrasion			1(0.8)
Lid margin discharge			1(0.8)
Epitheliopathy			3(2.5)
Ocular irritation			1(0.8)
Hyperemia		2(0.9)	
Ocular infiltrate			2(1.7)
Lid pain		1(0.4)	
Conjunctival staining		1(0.4)	

* Patient discontinued

All Nonocular Adverse Events in Bacterial Conjunctivitis Patient Population Regardless of Relationship: By Frequency

Event	0.5% LVFX (n=353) N(%)	0.3% OFLX (n=228) N(%)	Placebo (n=120) N(%)
Headache	14 (4.0)	6 (2.6)	2 (1.7)
Pharyngitis	5 (1.4)	1 (0.4)	
Fever	4 (1.1)	1 (0.4)	
Diarrhea	2 (0.6)	1 (0.4)	
Ear pain	2 (0.6)		
General pain	2 (0.6)	2 (0.9)	1 (0.8)
Infection (Cold/flu)	2 (0.6)	2 (0.9)	2 (1.7)
Rhinitis	2 (0.6)	2 (0.9)	
Sinusitis	2 (0.6)		
Bacterial infection	1 (0.3)		
Bronchitis	1 (0.3)		
Cough	1 (0.3)		
Dry skin	1 (0.3)		
Elevated pulse	1 (0.3)		
Facial edema	1 (0.3)		
Lethargy	1 (0.3)		
Nausea	1 (0.3)	1(0.4)	
Nose bleed	1 (0.3)		
Otitis	1 (0.3)		
Palpitations	1 (0.3)		
Rash	1 (0.3)	2(0.9)	
Sprained ankle	1 (0.3)		
Tooth pain	1 (0.3)		
Cyst		1(0.4)	
Edema		1(0.4)	
Enlarged lymph node			1(0.8)
Herpes zoster		1(0.4)	
Pneumonia			1(0.8)
Stomach ache			1(0.8)
Tinnitus		1(0.4)	
Tooth infection			1(0.8)

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

12 Conclusions

Studies #1 and #2 of this review provide a demonstration of the safety and efficacy of levofloxacin ophthalmic solution, 0.5% in the treatment of bacterial conjunctivitis. The submitted labeling is not supported.

13 Recommendations

1. Revised labeling consistent with this review should be submitted.
2. The applicant should commit to a 24 month expiration-dating period for the 5 mL fill size and an 18 month expiration-dating period for the 2.5 mL fill size based on data submitted to date.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 21-199
HFD-550
HFD-340/Carreras
HFD-550/Proj Mgr/Puglisi
HFD-830/CHEM/Khorshidi
HFD-590/MICRO/Dionne
HFD-805/MICRO/Pawar
HFD-550/PHARM/Mukherjee
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-199
Revised labeling and Safety Update

NDA #21-199		Submissions:	6/22/2000 & 8/6/00
M.O. Review #2		Review completed:	8/9/2000

Proposed trade name:	QUIXIN™
Generic name:	levofloxacin hemihydrate ophthalmic solution, 0.5%
Sponsor:	Santen Inc. 555 Gateway Drive Napa, CA 94558 (707) 254-1750
Pharmacologic Category:	Anti-infective (fluoroquinolone)
Proposed Indication(s):	Bacterial conjunctivitis
Dosage Form:	Ophthalmic solution
Route(s) of Administration:	Topical ophthalmic administration
NDA Drug Classification:	3 P
Related Drugs:	Ofloxacin ophthalmic solution Ciprofloxacin ophthalmic solution Norfloxacin ophthalmic solution
Related INDs:	[redacted] Levofloxacin ophthalmic solution (Santen)
Related NDAs:	NDA 20-634 Levaquin Tablets (levofloxacin tablets) NDA 20-635 Levaquin Injection

Safety Update:

"There has been no new safety information learned about the drug product which would reasonably affect ... No new clinical studies have been conducted since the submission of the NDA."

Reviewer's Comments: *Concur.*

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

Conclusions/ Recommendations

1. Revised labeling consistent with this review should be submitted.
2. The applicant should commit to a 24 month expiration-dating period for the 5 mL fill size and an 18 month expiration-dating period for the 2.5 mL fill size based on data submitted to date.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 21-199
HFD-550
HFD-340/Carreras
HFD-550/Proj Mgr/Puglisi
HFD-830/CHEM/Khorshidi
HFD-590/MICRO/Dionne
HFD-805/MICRO/Pawar
HFD-550/PHARM/Mukherjee
HFD-550/MO/Chambers

APPROVED THIS DAY
OF ORIGINAL

APPROVED THIS DAY
OF ORIGINAL

Medical Officer's Review of NDA 21-199
Revised labeling

NDA #21-199		Submissions:	8/15/2000
M.O. Review #3		Review completed:	8/15/2000

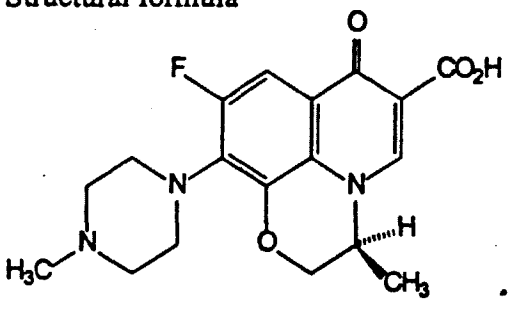
Proposed trade name:	QUIXIN™ (levofloxacin hemihydrate ophthalmic solution) 0.5%
Sponsor:	Santan Inc. 555 Gateway Drive, Napa, CA 94558 (707) 254-1750
Pharmacologic Category:	Anti-infective (fluoroquinolone)
Proposed Indication(s):	Bacterial conjunctivitis
Dosage Form:	Ophthalmic solution
Route(s) of Administration:	Topical ophthalmic administration
NDA Drug Classification:	3 P
Submitted:	Revised labeling based on comments from the Division.

QUIXIN™ (levofloxacin ophthalmic solution) 0.5%

DESCRIPTION

QUIXIN™ (levofloxacin ophthalmic solution) 0.5% is a sterile topical ophthalmic solution. Levofloxacin is a fluoroquinolone antibacterial agent, active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. Levofloxacin is the pure (-)-(S)-enantiomer of the racemic drug substance, ofloxacin. It is more soluble in water at neutral pH than ofloxacin.

Structural formula



levofloxacin hemihydrate

$C_{18}H_{20}FN_3O_4 \cdot ½ H_2O$ Mol Wt 370.38

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

DOSAGE AND ADMINSTRATION
Days 1 and 2: Instill one to two drops in the affected eye(s) every 2 hours while awake, up to 8 times per day.

Days 3 through 7: Instill one to two drops in the affected eye(s) every 4 hours while awake, up to 4 times per day.

HOW SUPPLIED
QUIXIN™ (levofloxacin ophthalmic solution) 0.5% is supplied in a white, low density polyethylene bottle with a controlled dropper tip and a tan, high density polyethylene cap in the following sizes:

2.5 mL- NDC 65086-135-25
5 mL - NDC 65086-135-05

Storage: Store at 15° – 25°C (59° – 77°F).

Rx Only.

Manufactured by:
Santen Oy, P. O. Box 33
FIN-33721 Tampere, Finland

Marketed by:
Santen Inc., Napa, CA 94558, U.S.A.

Licensed from Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan
U.S. PAT. NOS. 4,382,892; 4,551,456; 5,503,407
© Santen Inc.

Conclusions/ Recommendations
NDA 21-199, Quixin (levofloxacin ophthalmic solution) 0.5% for the treatment of bacterial conjunctivitis caused by susceptible strains with the labeling submitted on August 15, 2000, is recommended for approval from a clinical prospective.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 21-199
HFD-550
HFD-550/Proj Mgr/Puglisi
HFD-830/CHEM/Khorshidi
HFD-590/MICRO/Dionne
HFD-805/MICRO/Pawar
HFD-550/PHARM/Mukherjee
HFD-550/MO/Chambers