CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-571

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-571	Submission Date(s): May 01, 2003
Brand Name	PROPOSED BY THE SPONSOR IQUIX®
Generic Name	Levofloxacin 1.5% Ophthalmic Solution
Reviewer	Chandra S. Chaurasia, Ph. D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND division	ODE V (HFD-550)
Sponsor	Santen Incorporated, Napa, CA 94558
Relevant IND(s)	52,515 and 58,997
Submission Type; Code	New formulation, Higher Strength
Formulation; Strength(s)	Ophthalmic Solution, 1.5%
Indication	—

1. EXECUTIVE SUMMARY

EXECUTIVE SUMMARY

IQUIX™ (levofloxacin ophthalmic solution) 1.5% is a sterile topical ophthalmic solution developed by Santen Inc. for the treatment of bacterial corneal ulcers. Levofloxacin (LVFX), a fluoroquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance, ofloxacin, and possesses antibacterial activity against a broad spectrum of Gram-positive and Gram-negative ocular pathogens.

The proposed drug product does not contain any preservative. A lower strength of levofloxacin ophthalmic solution 0.5% (QUIXIN™, NDA 21-199, Santen, Aug 2000) is currently approved for the same therapeutic indication. Unlike the IQUIX, QUIXIN does contain benzalkonium chloride 0.005% as a preservative. The firm's rationale for developing the increased concentration is to provide an improved dosing regimen (less frequent dosing) while maintaining antimicrobial effect. The proposed dosing regimen for IQUIX is: [redacted]

Levofloxacin is also available as oral tablets in 750 mg, 500 mg and 250 mg strengths (NDA 20-634, Ortho McNeil), and as Injectable in 25 mg/mL and 5 mg/mL strengths (NDA 20-635, Ortho McNeil).

To support the Human Pharmacokinetics and Bioavailability section of this NDA, the sponsor has provided the results of a multiple dose pharmacokinetics study (Study No. 16-001) in healthy adult subjects. In this study, the systemic exposure of levofloxacin was determined following topical administration of 1.5% LVFX 1 dose (1-2 drops) per eye once in the morning on Day 1, 1 dose per eye every 2 hrs (total of 10 doses/day) on Days 2 to 8, 1 dose per eye every 4 hrs (total of 5 dosed/day) on Days 9 to 15 and 1 dose per eye once in the morning on Day 16.

The mean plasma concentration of LVFX one hour post-dose on Day 1 was 3.1 ng/mL, while that after 14 days of dosing ≥ 5 times per day collected one hour post-dose on Day 16 was 10.4 ng/mL. The $AUC_{0-\infty}$ and Cmax values for Day 1 dosing were 29.5±4.56 ng·hr/mL and 3.22±0.46 ng/mL, respectively. The corresponding values on Day 16 were 109±22.0 ng·hr/mL and 10.9 ±1.92 ng/mL, indicating a statistically significant ($p<0.002$) 3-fold increase on Day 16 in each case. It is noted that the reported $AUC_{0-\infty}$ and Cmax values of levofloxacin following a single oral dose of 500 mg are 47.7 µg hr/mL and 5.1 µg/mL indicating an overall systemic exposure following LVFX 1.5% ophthalmic administration approximately 1/400-times that after a single oral dose. Additionally, the mean plasma $t_{1/2}$ of 5.85 hr on Day 1 and 7.58 hr on Day 16 observed after ocular dosing is comparable to $t_{1/2}$ of 6.5 hr following oral administration suggesting a similar systemic elimination of levofloxacin after the oral and ophthalmic routes of administration.

The firm has also provided reports of study 16-006 that was conducted to evaluate safety and determine mean drug concentrations in the tears following topical ocular administration of 2 drops bilaterally once on Day 0, and 2 drops every two hours while awake on days 1-3 of 1.5% levofloxacin ophthalmic solution or 0.3% ofloxacin ophthalmic solution in healthy adult volunteers with asymptomatic eyes. At 12 hr after a single ocular dose on Day 0, the tear-concentration of LVFX was 24.2±28.5 µg/mL. Based on this observation, the sponsor concludes that the mean levofloxacin concentration in tears was not below 2 µg/mL—a concentration at or above the MIC_{90} for most ocular pathogens—12 hours after bilateral topical administration.

1.1. Comments to the Medical Officer:

To avoid potential interactions with other commonly prescribed ophthalmic solution products that patients may apply at the same time (e.g., ophthalmic solutions for treatment with glaucoma) please add a statement to the PREACAUTION SECTION stating that

1.2. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to the Human Pharmacokinetics and Biopharmaceutics Section of NDA 21-571. The information submitted under this section is acceptable.

_____ Date: _____

Chandra S. Chaurasia, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

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SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The proposed product IQUIX® (levofloxacin ophthalmic solution) 1.5% is a self-preserved sterile topical ophthalmic solution developed by Santen Inc. for the treatment of bacterial corneal ulcers. Each mL of IQUIX contains 15.36 mg of levofloxacin hemihydrate equivalent to 15 mg levofloxacin. In addition, the formulation contains glycerin and water as the inactive ingredients, and may also contain hydrochloric acid and/or sodium hydroxide to adjust pH. As stated by the firm, the high concentration of anti-infective maintains product sterility (US APE [United States Pharmacopoeia Antimicrobial Preservative Effectiveness] requirements) without an additional preservative.

The drug product is intended for the treatment of bacterial corneal ulcers. A lower strength of IQUIX, levofloxacin ophthalmic solution 0.5% (QUIXIN™) is currently approved for the same therapeutic indication.

The firm's rationale for developing the increased concentration is to provide an improved dosing regimen (less frequent dosing) while maintaining antimicrobial effect. The proposed dosing regimen for IQUIX is: [redacted]

To support the Human Pharmacokinetics and Bioavailability section of this NDA, the sponsor has provided the results of the following two multiple dose pharmacokinetics studies both conducted in healthy adult subjects:

Study No. 16-001: A 21-Day, randomized, double-masked, placebo-controlled, single-center study evaluating safety, comfort, and pharmacokinetics of 1.5% levofloxacin ophthalmic solution in healthy adult volunteers.

Study No. 16-006: A randomized, double-masked, single-center trial evaluating safety and mean drug concentration in tears following topical administration of 1.5% levofloxacin ophthalmic solution (1.5% LVFX) or 0.3% ofloxacin ophthalmic solution (0.3% OFLX) in healthy adult volunteers with asymptomatic eyes.

The above studies were reviewed in detail. The systemic exposure and pharmacokinetic parameters were obtained from Study No. 16-001. The appropriate values from this study have been cited in the labeling. Although the sponsor may have conducted such study as part of its levofloxacin 0.5% ophthalmic solution under the approved Quixin NDA, the sponsor is recommended to submit information relevant to the current study.

Study 16-006 was conducted to determine comparative tear concentrations of the proposed drug and the currently marketed ofloxacin ophthalmic solution 0.3%, and also to measure if the mean levofloxacin concentration in tears was not below 2 μg/mL—a concentration at or above the MIC_{90} for most ocular pathogens—12 hours after bilateral topical administration .

In addition, the firm has also conducted two Phase II/III safety and efficacy studies: No. 16-002 in adults and children (US study) and No. 16-003 in adults (in Brazil, India, and Israel) with suspected bacterial corneal ulcer. No pharmacokinetic sampling was obtained in these studies.

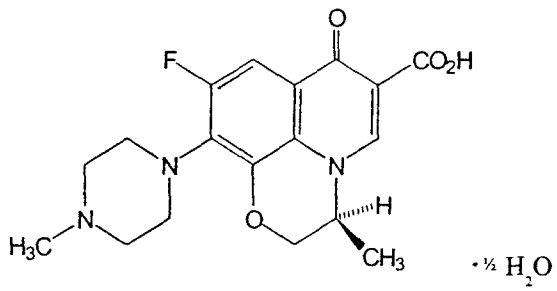
4. QUESTION-BASED REVIEW

4.1. General Attributes

4.1.1. What are the highlights of the physicochemical properties of levofloxacin ophthalmic solution 1.5%?

IQUIX® (levofloxacin ophthalmic solution) 1.5% is a sterile topical ophthalmic solution. Levofloxacin is a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure. Each mL of IQUIX® contains 15.36 mg of levofloxacin hemihydrate equivalent to 15 mg levofloxacin. Levofloxacin is the pure (-)-(*S*)-enantiomer of the racemic drug substance, ofloxacin.

Structural formula



levofloxacin hemihydrate

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

Chemical Name: (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4 benzoxazine-6-carboxylic acid hemihydrate.

Physicochemical Properties: Levofloxacin (hemihydrate) is a yellowish-white crystalline powder. It is more soluble in water at neutral pH than ofloxacin.

IQUIX® solution is isotonic and formulated at pH 6.5 with an osmolality of approximately 290 mOsm/kg. It is a preservative free formulation containing levofloxacin 1.5% (15 mg/mL) as the active ingredient with water and glycerin as inactives. The formulation may also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

4.1.2. What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of levofloxacin ophthalmic solution 1.5%?

Indication: IQUIX® solution is indicated for the treatment of corneal ulcer caused by susceptible strains of gram-positive and gram-negative bacteria.

Dosage and Route of Administration: The recommended dose of levofloxacin ophthalmic solution 1.5% is as follow:

[redacted]

Mechanism of Action: The mechanism of action of levofloxacin involves the inhibition of bacterial topoisomerase IV and DNA gyrase, enzymes required for DNA replication, transcription, repair, and recombination.

4.2. General Clinical Pharmacology

4.2.1. Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

For Study No. 16-001: The active parent moiety in the plasma samples were analyzed by validated LC/MS/MS method with a detection limit of [redacted]. The assay was validated over the levofloxacin concentration range of [redacted]

For Study No. 16-006: Tear samples were collected using tear strips and analyzed by validated HPLC method with an LOQ of [redacted] (Study 16-006) with a detection limit of [redacted]

Please refer to Section 4.6 for summary details on analytical methods.

4.2.2. Are the study populations relevant to the proposed indication?

The pharmacokinetic studies following ocular administrations were done in adult healthy Caucasian and Non Caucasian volunteers to assess bioavailability of the drug product. Levofloxacin is indicated for the treatment of corneal ulcer caused by susceptible strains of bacteria. Although the appropriate study population would have been subjects with corneal ulcers, given the known pharmacokinetics of the drug substance, from safety and efficacy point of view, it is unlikely that subjects with corneal ulcer would have had any significantly different exposure to the test product than that in the healthy subjects.

4.3. Intrinsic Factors: Age, Gender, Race, and Disease States.

Pediatric Use:

Safety and effectiveness of levofloxacin ophthalmic solution 1.5% in children have not been established. The Sponsor had requested for a full waiver of pediatric studies (IND 58,997, submission dated Jan 10, 2003, M1-V01-043). Oral administration of systemic quinolones including levofloxacin has been shown to cause arthropathy in juvenile animals of several species.

The sponsor's proposed labeling states, "*safety and effectiveness in children below the age of [redacted] have not been established.*" However, it is noted that the pivotal PK study (Report No. 16-001) included only adults population (22 to 72 years old). In the labeling, this reviewer has therefore recommended deletion of this statement (please refer to Section 5).

Geriatric Use:

The pivotal PK study (plasma) included healthy volunteers in the age range of 22-72 years of age. Only two of the 14 subjects in the drug-treatment group were 65 years or older. Thus, no significant PK information could be obtained on the difference between young and elderly population following ophthalmic administration. However, it is noted that the package insert for

orally administered levofloxacin states that the pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration

Gender and Race:
Of the 14 subjects (8 Caucasians and 6 Non Caucasians) in the drug treatment group in study 1600-01, there were 5 females and 9 males. Although, no statistical analysis were carried out, the differences in the mean plasma levofloxacin concentration of levofloxacin seen were small with no significant clinical significance.

Hepatic Impairment:
Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

4.4. **Extrinsic Factors:** Drugs, Diets and Smoking

Drug Interactions:
Specific drug interactions have not been conducted with levofloxacin ophthalmic solution 1.5%. The proposed labeling of levofloxacin ophthalmic solution 1.5% and the labeling of the approved Quixin (levofloxacin ophthalmic solution, 0.5%) indicate that the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly. Since the overall systemic exposure following levofloxacin 1.5% ophthalmic administration is approximately 1/400 times that of oral 500 mg dose, these drug-drug interactions may not be of clinical significance for conducting specific drug interaction studies with the levofloxacin 1.5% ophthalmic solution.

Additionally, potential interactions with other commonly prescribed ophthalmic solution products that patients may apply at the same time (e.g., ophthalmic solutions for the treatment of glaucoma) may be addressed by adding a statement to the PRECAUTIONS SECTION stating that "

Diet and Smoking:
Considering the route of administration and dosage regimen, no significant effect of diet or smoking is anticipated on the PK of levofloxacin ophthalmic solution 1.5%.

4.5 General Biopharmaceutics

4.5.1. What are the differences between clinical and to-be-marked formulations?
As reported by the firm, the final drug product has the following formulation.
Table: Component and Compositions of Levofloxacin 1.5% ophthalmic Solution.

Ingredients	Percentage w/v	mg/mL
Levofloxacin[1]	1.5	15.0
Glycerin, USP		
Dilute Hydrochloric acid and/or Dilute Sodium Hydroxide, USP	Adjust to target pH 6.5	
Purified Water, USP		

[1] *The hemidrate of levofloxacin was used. The content of levofloxacin hemihydrate is reported as 15.36 mg/mL.*

In the Phase I pivotal PK study, the placebo solution also contained 0.0025% of benzalkonium chloride as preservative. This preservative is not present in the test drug formulation.

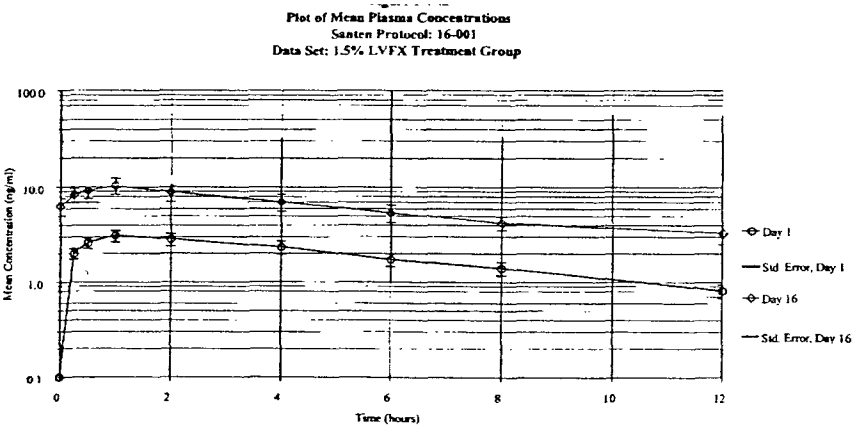
The concentrations of the levofloxacin solution used in all clinical studies is the same i.e., 1.5%. The batch no. used in the PK studies 16-001 and 16-006 is 1017S with no preservative in the formulation.

4.5.2. Pharmacokinetic Data

Summary of the Study 16-001 (Plasma Study):
This was a 21-day, randomized, double-masked, placebo-controlled, single-center study to evaluate the safety, comfort, and plasma concentrations of levofloxacin (LVFX) following topical administration of 1.5% LVFX ophthalmic in healthy, adult subjects with asymptomatic eyes. The dosing schedule was 1-2 drops per eye once in the morning on Days 1 and 16; 1-2 drops per eye every two hours Days 2 through 8; and 1-2 drops per eye every four hours Days 9 through 15. The summary of pharmacokinetic parameters is given in the Table below. Figure 1 depicts Day 1 and Day 16 mean plasma concentration profile following administration of levofloxacin 1.5%:

PK Parameter	Day 1	Day 16	p-value
$AUC_{0\text{-}12}$ (ng·hr/mL) Mean ±SE Range	 22.1±3.25 8.84-42.0	 71.9±13.4 18.6-210	 0.002
$AUC_{0\text{-}\infty}$(ng·hr/mL) Mean SE Range	 29.5±4.56 10.9-71.2	 109±22.0 25.4-329	 0.002
Cmax (ng/mL) Mean SE Range	 3.22±0.46 1.32-6.33	 10.9 ±1.92 3.13-27.9	 0.001
Tmax (hr) Mean SE Range	 1.07±0.12 0.50-2.00	 0.77±0.13 0.25-2.00	 0.116
$T_{1/2}$ (hr) Mean SE Range	 5.85± 0.50 3.92-10.2	 7.58±0.58 5.03-11.8	 0.011

Figure 1.
Is levofloxacin 1.5% ophthalmic solution absorbed after topical ophthalmic administration?



There is demonstrable systemic exposure of levofloxacin following ocular administration. The mean plasma concentration of LVFX one hour post-dose on Day 1 was 3.1 ng/mg, while that after 14 days of dosing ≥ 5 times per day collected one hour post-dose on Day 16 was 10.4 ng/mL. The $AUC_{0-\infty}$ and Cmax values for Day 1 dosing were 29.5±4.56 ng·hr/mL and 3.22±0.46 ng/mL, respectively. The corresponding values on Day 16 were 109±22.0 ng·hr/mL and 10.9 ±1.92 ng/mL, indicating a statistically significant ($p<0.002$) 3-fold increase on Day 16 in each case.

How do the plasma levels of levofloxacin absorbed after topical ophthalmic administration of levofloxacin 1.5% ophthalmic solution compare to those from oral administration of levofloxacin?

The reported $AUC_{0-\infty}$ and Cmax values of levofloxacin following a single oral dose of 500 mg are 47.7 µg hr/mL and 5.1 µg/mL. This indicates that an overall systemic exposure following LVFX 1.5% ophthalmic administration is approximately 1/400-times than that after a single oral dose of 500 mg levofloxacin. However, the mean plasma $t_{1/2}$ of 5.85 hr on Day 1 and 7.58 hr on Day 16 observed after ocular dosing is comparable to $t_{1/2}$ of 6.5 hr following oral administration suggesting a similar systemic elimination of levofloxacin after the oral and ophthalmic routes of administration.

How do the plasma levels of levofloxacin absorbed after topical ophthalmic administration of the proposed test product (1.5% strength) compare to those from topical ophthalmic administration of the approved levofloxacin 0.5% strength?
During a 15-day course of treatment with Quixin solution (levofloxacin ophthalmic solution 0.5%), the mean levofloxacin concentration in plasma 1-hour post dose ranged form 0.86 ng/ml on Day 1 to 2.05 ng/mL on Day 15. The highest maximum mean levofloxacin concentration of 2.25 ng/mL was measured on Day 4 following 2 days of dosing every 2 hours for a total of 8 doses per day. Maximum mean levofloxacin concentrations increased from 0.94 ng/mL on Day 1 to 2.15 ng/mL on Day 15, which is about 4-5 times lower than those observed with the test product.

Study 16-006 (Tear): This was a randomized, double-masked, single center trial evaluating safety and mean drug concentration in tears following topical administration of 1.5% levofloxacin ophthalmic solution (1.5% LVFX) or 0.3% ofloxacin ophthalmic solution (0.3% OFLX) in healthy adult volunteers with asymptomatic eyes.

The objective of this study was to evaluate safety and determine mean drug concentration in tears following topical administration of 1.5% levofloxacin ophthalmic solution 1.5% or 0.3% ofloxacin ophthalmic solution in healthy adult volunteers with asymptomatic eyes.

This study was conducted for 16 days in 125 healthy adult volunteers with asymptomatic eyes. On Day 0, 100 of the 125 subjects (80%) and 25 (20%) received one dose (two drops) bilaterally of 1.5% levofloxacin and 0.3% floxacin, respectively. Tear samples were collected from both eyes of all subjects in each group using Schirmer strips as follows: Group A: 0.25, Group B: 2, Group C: 6, Group D:12 and Group E: 24 hours post dose with 20 subjects from the 1.5% LVFX

group and 5 subjects from the 0.3% OFLX group at each sampling time. On days 1-3 subjects instilled one dose bilaterally every 2 hours while awake and 4 and 6 hours after retiring, totaling 10 doses per day. On Days 4-14, subjects instilled one dose 4 times daily while awake. A morning pre-dose tear sample was taken on Day 4 and an Exit tear sample was taken the morning of Day 15.

Results of the study are summarized in the Table below:

Sampling Time point	Treatment			
	1.5% Levofloxacin		0.3% Ofloxacin	
	N	Mean SD (µg/mL)	N	Mean SD (µg/mL)
Day 0, Hour 0.25	20	757±767	5	75.7±101
Day 0, Hour 2	20	439±552	5	43.2±34.3
Day 0, Hour 6	19	157±185	5	41.5±44.6
Day 0, Hour 12*	19	24.2±28.5	5	6.9±5.4
Day 0, Hour 24	18	12.7±25.0	4	2.3±1.9
Day 4, Pre-dose	85	126±252	22	12.6±17.4
Day 15, Hour 2	94	70.4±177	25	25.4±78.0

*p=0.022, for the null hypothesis that the means for 1.5% LVFX and 0.3% OFLX are equal

The results show that the tear concentrations of LVFX were higher than those of OFLX at all time points. At 12 hr after a single ocular dose on Day 0, the concentration of LVFX was approximately 4-times higher than that of OFLX (p=0.022).

Reviewer's Note: *The sponsor has also provided estimated PK parameters (AUC0-12, Cmax and T1/2) for Day) samples for the treatment drugs, based on modeling and simulation. Since, results of this will not have any impact on the study outcome, evaluation of these estimated PK parameters were not deemed necessary by this reviewer.*

4.6. Analytical

4.6.1. What analytical method was used to determine levofloxacin plasma concentration? Has the analytical method been fully validated?

For Study No. 16-001: Plasma samples were analyzed by validated LC/MS/MS method with a detection limit of ——— The assay was validated over the levofloxacin concentration range of ——— .. The inter assay precision and accuracy for the LOQ and QC samples ranged from ——— and ——— respectively. The recovery ranged from 81.2 to 99.0% with the internal standard ——— recovery of 63.5 to 81.4%. The ———) stability studies were found acceptable. The method was fully validated with respect to precision, accuracy, specificity and ——— stability. However, a ——— has not been submitted. This has been addressed in the Comments to Sponsor (please refer to Section 1, page 3). The analytical method validation summary and details are provided in Module 2, Vol. 01-121 and Module 5 Vol. 02, pp. 379, respectively.

4.6.2. What analytical method was used to determine levofloxacin tear concentration? Has the analytical method been fully validated?

For Study No. 16-006: Tear samples were collected using tear strips and analyzed by validated HPLC method with an LOQ of [redacted] Study 16-006) with a detection limit of [redacted] Each strip had been determined to hold approximately 10 µL volume of tears. The assay was validated over the levofloxacin concentration range of [redacted]. The intra assay precision and accuracy for the LOQ were 10.5% and -16.6%, respectively. The inter assay precision and accuracy for the QC samples ranged from 1.7 to 13.1% and -19.6 to 1.9%, respectively. The recovery ranged from 83.9 to 95.9%. with the internal standard ([redacted]) recovery of 63.5 to 81.4%. The [redacted] stability studies were found acceptable. The analytical method validation summary and details are provided in Module 2, Vol. 01-122 and Module 5 Vol.05-1245, respectively. The firm has provided acceptable data for [redacted] long term stability of levofloxacin in human tears on Schirmer Strips at [redacted].

7 Draft Labeling Page(s) Withheld

6.2. Individual Study Review

6.2.1. Study No. 16-001: A 21-Day, randomized, double-masked, placebo-controlled, single-center study evaluating safety, comfort, and pharmacokinetics of 1.5% levofloxacin ophthalmic solution in healthy adult volunteers.

Clinical Site: Investigator: —
Name of the Firm: —
Study Dates: Start Oct 30, 1999 End: Nov 23, 1999.
Analytical Site: —

This was a 21-day, randomized, double-masked, placebo-controlled, single-center study to evaluate the safety, comfort, and plasma concentrations of levofloxacin (LVFX) following topical administration of 1.5% LVFX ophthalmic in healthy, adult subjects with asymptomatic eyes. The study subjects (N=30, 14 test and 16 vehicle) ranged in age from 20-72 years (mean 43 years), 17 (57%) males and 13 (43%) females, 16 Caucasians (53%) and 14 Non-Caucasian (47%, ***please note: breakdown of the racial profile has not been provided in the submission***). The subjects were randomly assigned to receive either 1.5% LVFX or placebo per the following dosing schedule:

Day(s)	Number of drops
1	1 dose (1-2 drops) per eye once in the morning
2 to 8	1 dose per eye every 2 hours (total of 10 doses per day)
9 to 15	1 dose per eye every 4 hours (total of 5 doses per day)
16	1 dose per eye once in the morning

Subjects' inclusion and exclusion criteria are given in Module5, Vol. 01-008 and 123-125.
The test drug used was from Lot No. D99719 (formulation no. 1017S) without benzalkonium chloride (BAK) preservative. The placebo used was preserved with BAK 0.0025%

Plasma samples were collected on Days 1 and 16 prior to administration of drug and at 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hr post-dose. In additions, pre dose samples were collected on Days 2 and 9. Twenty-eight subjects completed the study. One subject (#1124) in the test drug group was withdrawn from the study due to a non-ocular adverse event-cellulitis on right arm. The event was considered to be unrelated to the study drug. Subject #1103 was withdrawn in the placebo group due to 9 AEs in 11 days, all of which judged to be unlikely related to study medication.
PK parameters were calculated from a non-compartmental model using WinNonLin software and compared between Days 1 and 16 statistically using a 2-tailed t-test. A p-value < 0.05 considered statistically significant. The summary of pharmacokinetic parameters is given in the Table below:

PK Parameter	Day 1	Day 16	p-value
AUC_{0-12} (ng·hr/mL)			
Mean ±SE	22.1±3.25	71.9±13.4	0.002
Range	8.84-42.0	18.6-210	
$AUC_{0-\infty}$(ng·hr/mL)			
Mean SE	29.5±4.56	109±22.0	0.002
Range	10.9-71.2	25.4-329	
Cmax (ng/mL)			
Mean SE	3.22±0.46	10.9 ±1.92	0.001
Range	1.32-6.33	3.13-27.9	
Tmax (hr)			
Mean SE	1.07±0.12	0.77±0.13	0.116
Range	0.50-2.00	0.25-2.00	
$T_{1/2}$ (hr)			
Mean SE	5.85± 0.50	7.58±0.58	0.011
Range	3.92-10.2	5.03-11.8	

Overall, 19/30 (63%) subjects reported 58 AEs, 11/16 969%) in the placebo group and 8/14 (57%) in the LVFX group. These AEs were mild to moderate in severity and most resolved without treatment. Overall, 8/30 (27%) subjects (1/16 or 6% in the placebo and 7/14 or 50% in the test drug group) reported an abnormal taste after dosing. The event was considered possibly related to the test drug product by the investigator.

After 14 days of dosing ≥ 5 times per day, mean plasma concentration of levofloxacin collected one hour post-dose on Day 16 (10.4 ng/mL) was higher than on Day 1 (3.1 ng/mL) indicating a dose-dependent change in mean LVFX plasma concentration. There was a statistically significant ($p < 0.002$) 3-fold increase in AUC and Cmax from Day 1 to Day 16. The reported AUC0-inf and Cmax values of levofloxacin following a single oral dose of 500 mg are 47.7 µg hr/mL and 5.1 µg/mL, indicating an overall systemic exposure of approximately 400-times less than that after a single oral dose. Additionally, the mean plasma t1/2 of 6.5 hr is comparable to that observed after ocular dosing (5.85 hr Day 1 and 7.58 hr Day 16). This suggests a similar systemic elimination of the oral and ophthalmic routes of administration.

6.2.2. Study No. 16-006: A randomized, double-masked, single-center trial evaluating safety and mean drug concentration in tears following topical administration of 1.5% levofloxacin ophthalmic solution (1.5% LVFX) or 0.3% ofloxacin ophthalmic solution (0.3% OFLX) in healthy adult volunteers with asymptomatic eyes. .

The objective of this study was to evaluate safety and determine mean drug concentration in tears following topical administration of 1.5% levofloxacin ophthalmic solution 1,5% or 0.3% ofloxacin ophthalmic solution in healthy adult volunteers with asymptomatic eyes. From bioavailability perspective the two hypotheses for this study were:

- The mean levofloxacin concentration in human tears will not be below 2 mg/mL, a concentration at or above the MIc90 for most ocular pathogens, 12 hors after bilateral topical administration.
- The mean levofloxacin concentration in human tears will be greater than the ofloxacin concentration 12 hours after bilateral topical administration.

Clinical Site: Investigator: —
Name of the Firm: —
Analytical Site: —

This study was conducted for 16 days in 125 healthy adult volunteers with asymptomatic eyes. The study subjects ranged in age from 18-69 years (mean 33 years), 29 (23%) males and 77 (77%) females, 83 Caucasians (66%), 24 Hispanics (19%), 16 Blacks (13%) and 2 Asian (2%). On Day 0, 100 of the 125 subjects (80%) and 25 (20%) received one dose (two drops) bilaterally of 1.5% levofloxacin and 0.3% floxacin, respectively. Tear samples were collected from both eyes of all subjects in each group using Schirmer strips at as follows: Group A: 0.25, Group B: 2, Group C: 6, Group D:12 and Group E: 24 hours post dose with 20 subjects from the 1.5% LVFX group and 5 subjects from the 0.3% OFLX group at each sampling time. On days 1-3 subjects instilled one dose bilaterally every 2 hours while awake and 4 and 6 hours after retiring, totaling 10 doses per day. On Days 4-14, subjects instilled one dose 4 times daily while awake. A morning pre-dose tear sample was taken on Day 4 and an Exit tear sample was taken the morning of Day 15. Safety assessments

included adverse events, visual acuity tests, ocular symptoms, biomicroscopic and ophthalmoscopic findings and Rose Bengal staining.

The tear samples were assayed for levofloxacin and ofloxacin concentrations using a validated HPLC assay.

Results of the study are summarized in the Table below:

Sampling Time point	Treatment			
	1.5% Levofloxacin		0.3% Ofloxacin	
	N	Mean SD (µg/mL)	N	Mean SD (µg/mL)
Day 0, Hour 0.25	20	757±767	5	75.7±101
Day 0, Hour 2	20	439±552	5	43.2±34.3
Day 0, Hour 6	19	157±185	5	41.5±44.6
Day 0, Hour 12*	19	24.2±28.5	5	6.9±5.4
Day 0, Hour 24	18	12.7±25.0	4	2.3±1.9
Day 4, Pre-dose	85	126±252	22	12.6±17.4
Day 15, Hour 2	94	70.4±177	25	25.4±78.0

*p=0.022, for the null hypothesis that the means for 1.5% LVFX and 0.3% OFLX are equal

The results show that the tear concentrations of LVFX were higher than those of OFLX at all time points. At 12 hr after a single ocular dose on Day 0, the concentration of LVFX was approximately 4-times higher than that of OFLX (p=0.022).

Adverse Events: There were no notable differences between 1.5% LVFX and 0.3% OFLX in the incidence of overall adverse events or treatment-related AEs. The most frequently reported non-ocular AEs in the 1.5% LVFX group were dysgeusia 14%, 14/100) and headache (11%, 11/100). In the 0.3% OFLX group, the most frequently reported AE was headache (12%, 3/25). Ocular AEs were limited to only one (1%, 1/100) I the LVFX group, heavy eye sensation, and 2 (8%, 2/25) I the OFLX group, dry eyes and eyelid margin crusting.
Based on the above results the sponsor concluded that:

- The mean levofloxacin concentration in tears was not below 2 µg/mL, a concentration at or above the MIC_{90} for most ocular pathogens, 12 hours after bilateral topical administration.
- The mean levofloxacin concentration in tears was greater than the ofloxacin concentration 12 hours after bilateral topical administration.

Reviewer's Note: *The sponsor has also provided estimated PK parameters (AUC0-12, Cmax and T1/2) for Day) samples for the treatment drugs, based on modeling and simulation. Since, results of this will not have any impact on the study outcome, evaluation of these estimated PK parameters were not deemed necessary by this reviewer.*

6.3. OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics NEW DRUG APPLICATION FILING AND REVIEW FORM			
1.1.1.5.1 General Information About the Submission			
	Information		Information
NDA Number	21-571	Brand Name	**PROPOSED BY THE SPONSOR:** *In order of preference:* IQUIX®
OCPB Division (I, II, III)	DPE III, HFD 880	Generic Name	Levofloxacin 1.5% Ophthalmic Solution
Medical Division	ODE V, HFD 550	Drug Class	Fluoroquinolone Antibacterial
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Ophthalmic Solution
		Dosing Regimen	[redacted]
Related INDs	52,515 and 58,997		
Date of Submission	May 01, 2003	Route of Administration	Topical Ocular administration
Estimated Due Date of OCPB Review	Sep 01, 2003	Sponsor	Santen Incorporated Napa, CA 94558
PDUFA Due Date	March 01, 2004	Priority Classification	
1.1.1.6 Division Due Date			

1.1.1.6.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
multiple dose:	X	2		Report No. 16-001: Safety and PK in healthy adult volunteers (N=30, males and females, 20-72 yr.) Report No. 16-006: Safety and drug concentrations in tears compared to ofloxacin 0.3% ophthalmic solution in adult healthy volunteers.
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			Pooled Data
pediatrics:				The Sponsor had requested for a full waiver of pediatric studies (IND 58,997, submission dated Jan 10, 2003, M1-V01-043)
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				

(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**34**		On PK and Safety/Efficacy evaluations
Total Number of Studies		**4**		Two in healthy adults with PK data, and 2 in patients for safety and efficacy evaluation
1.1.1.6.1.2				

1.1.1.6.1.3 Filability and QBR comments

1.1.1.7	**"X" if yes**	1.1.1.7.1.1.1.1.1 Comments
1.1.1.8 Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
1.1.1.9 Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• ***What are the highlights of the physicochemical properties of levofloxacin 1.5% ophthalmic solution?*** • ***What are the properties of the formulation of the drug product? What are the differences between clinical and to-be-marked formulations?*** • *What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of levofloxacin 1.5% ophthalmic solution?* • *Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?* • Are analytical methods sensitive enough to determine the extent of levofloxacin absorption after topical ophthalmic administration? • Is levofloxacin 1.5% ophthalmic solution absorbed after topical ophthalmic administration? • How do the plasma levels of levofloxacin absorbed after topical ophthalmic administration of levofloxacin 1.5% ophthalmic solution compare to those from oral, IV and administration of levofloxacin? • How do the plasma levels of levofloxacin absorbed after topical ophthalmic administration of the proposed test product (1.5% strength) compare to those from topical ophthalmic administration of the approved levofloxacin 0.5% strength?	

Other comments or information not included above	• Levofloxacin has been approved as ophthalmic solution in 0.5% strength under the trade name QUIXIN™ indicated for the treatment of bacterial conjunctivitis and manufactured by SANTEN, sponsor of this NDA. • In addition, in the US levofloxacin is also available as injectable 25mg/mL, 500 mg/100mL strengths, and as oral dosage form in 250 mg, 500 mg and 750 mg strengths. Information with regards to pharmacokinetic studies involving intrinsic and extrinsic factors and geriatric population is available that will be ascertained at the time of review of the current submission. • The sponsor has submitted two clinical studies (Protocol No. 16-002, 16-003R) comparing safety and efficacy of 1.5% levofloxacin with 0.3% ofloxacin. These studies are not relevant from bioavailability and pharmacokinetics perspective.
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**
Secondary reviewer Signature and Date	**E. Dennis Bashaw, Pharm. D.**

CC: NDA 21-571, HFD-850 (P. Lee), HFD-550 (L. Gorski), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chandra S. Chaurasia
12/23/03 03:13:17 PM
BIOPHARMACEUTICS

Thanks again.

Dennis Bashaw
12/24/03 02:56:42 PM
BIOPHARMACEUTICS