CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-199

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-199 SUBMISSION DATE: 3/1/00, 5/31/00

PRODUCT: QUIXIN®
(Levofloxacin Ophthalmic Solution, 0.5%)

SPONSOR: Santen Incorporated
Napa, CA

REVIEWER: Veneeta Tandon, Ph.D.

REVIEW OF A NDA

I. BACKGROUND

Drug Classification: 3P

Dosage Form: Ophthalmic solution for topical application (Levofloxacin, 0.5% or 5 mg/mL)

Indication: For the treatment of bacterial conjunctivitis in both adults and children 1 year of age and older.

Pharmacologic Class: Fluoroquinolone antibacterial active against abroad spectrum of Gram-positive and Gram-negative ocular pathogens. Levofloxacin is the pure (-)-S-enantiomer of the racemic drug substance, ofloxacin.

Dosage and Administration: Days 1 and 2: One to two drops in the affected eye(s) every 2 hours while awake up to 8 times per day.
Days 3 through 5: One to two drops in the affected eye(s) every 4 hours while awake up to 4 times per day.
QUIXIN® can be administered safely up to 15 days.

Foreign Marketing History: Levofloxacin in the same formulation as this application is not marketed in any country. However, Santen Pharmaceutical Co., Ltd. (Santen Ltd) recently received approval to market a 0.5% levofloxacin ophthalmic solution in Japan (by the name Cravit ™) for various external ocular infections. The ophthalmic product approved in Japan is the same as that which is being proposed for approval under this NDA with the

exception that it does not contain the preservative benzalkonium chloride.
Levaquin® Tablets and Injection (NDA 20-634 and 20-635) By RW Johnson are approved in the U.S at a dose of 250-500 mg every 24 hours. Systemic formulations of levofloxacin is available worldwide.

Formulation: The composition of levofloxacin ophthalmic solution is given below (Formula 1014S), the osmolality of the solution is 300 mOsm/kg:

Ingredient	mg/mL
Levofloxacin hemihydrate [1]	5.12
Benzalkonium chloride, NF	0.05
Sodium Chloride, USP	
Sodium hydroxide, NF, 0.1N and/or Hydrochloric acid, NF, 0.1N	
Purified Water, USP	

[1] each mL contains 5 mg levofloxacin equivalent to 5.12 mg levofloxacin

II. RECOMMENDATION

This application is acceptable from the standpoint of clinical pharmacology and biopharmaceutics requirement. The labeling recommendations suggested on page 7-8 of this review should be incorporated in the label for QUIXIN® Ophthalmic solution.

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III. ANALYTICAL VALIDATION

The analytical validation of levofloxacin in human plasma and tears is acceptable.

Levofloxacin in human plasma:

Levofloxacin in Human Tears:

IV. PHARMACOKINETIC STUDIES

The sponsor has submitted three studies to support their application. Study 03-005 where levofloxacin concentrations have been determined in the plasma after topical administration has been carried out with the appropriate dosage regimen as well as the to-be-marketed formulation. Study 95034 is Phase I study, where levofloxacin concentrations have been determined in the serum. In support of the antibacterial activity of levofloxacin, the sponsor has also evaluated the levofloxacin concentrations in human tears.

Is levofloxacin absorbed systemically upon topical application to the eye? If yes. will there be a safety concern based on systemic levels of levofloxacin?

Yes, Levofloxacin is systemically absorbed upon topical application to the eye at the to-be-marketed regimen. The study results are described below, with the question being addressed in the Reviewer's comment/conclusion.

A Two-week, Open-Label, Single-Center Trial of Plasma Drug Concentrations Following Administration of 0.5% Levofloxacin Ophthalmic Solution in Healthy Volunteers (Study Report 03-005)

The plasma concentration of levofloxacin was evaluated in 15 healthy subjects (9F & 6M, age range 19-68 years, 14 Caucasian and 1 Asian). Levofloxacin ophthalmic solution 0.5% (lot 73821) was administered as per the proposed label, i.e

Day 1 and 15: Single dose of two drops in each eye
Days 2 and 3: Two drops per eye 8x/day at 2-hour intervals
Days 4-14: Two drops per eye 4x/day at 4-hour intervals

Blood samples:

Day 1 and 15: pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hours dose.
Days 4 and 6: pre-dose and 1 hour post dose

Pharmacokinetic evaluation:

All post-dosing plasma levofloxacin concentrations were above the limit of quantitation (0.1 ng/mL) till 8 hours. Plasma samples were not taken beyond 8 hours. The pharmacokinetic parameters on Day 1 and Day 15 are shown in the following Table. Individual subject pharmacokinetic parameters are attached in the Appendix on page 10.

Parameters	**Day 1 N=15**		**Day 15 N=15**		**p-value**
	Mean (SD)	Range	Mean (SD)	Range	
AUC(0-8), ng.h/mL	5.01(2.04)		12.06(5.36)		<0.001
Cmax (ng/mL)	0.94(0.47)		2.15(1.00)		<0.001
Tmax (hr)	0.64(0.49)		0.93(0.60)		0.088
T1/2 (hr)	7.01(7.17)		7.61(2.16)		0.759

The mean levofloxacin concentrations at 1 hour post-dose is shown in the following table:

Levofloxacin (ng/mL)	Day 1	Day 4	Day 6	Day 15
Mean (SD)	0.86 (0.37)	2.25(0.96)	1.76(0.81)	2.05(1.03)

Observations:

- The C_{max} and AUC increased by 2.3-2.5x with multiple dosing up to 14 days

- There was a marginal increase in T_{max}, though the difference was not statistically significant.
- There was no change in $t_{1/2}$.
- The maximum observed concentration on multiple dosing was 4.78 ng/mL and the maximum mean concentration (2.25±0.96) was observed at 1-hour post-dose on Day 4.

Reviewer's Comment/Conclusion:

- The 2.3-2.5x increase in C_{max} and AUC with topical dosing would not be a safety concern for topical levofloxacin ophthalmic solution because levofloxacin is also taken orally at much higher doses and the peak concentration observed after topical dosing is only a very small fraction of that observed after oral dosing. Discussions regarding comparison to the oral and IV dose is given in the subsequent bullets.

- Considering the drop size to be approximately 35 µL [redacted] as per chemistry review by Dr. H. Korshidi), the total volume administered per dose (i.e. 2 drops in each eye) would be 140 µL. This would amount to a dose of 0.7 mg of levofloxacin per dose. For days 1-2, this would be 5.6 mg/day and for the remaining days it would be 2.8 mg/day. The maximum duration of treatment with levofloxacin ophthalmic solution is 15 days. The oral/IV dose for levofloxacin is 250-500 mg/day. The topical dose of levofloxacin is approximately 50-200 times lower than that of the oral/IV dose.

- The mean peak plasma concentration after 14 days of topical dosing with levofloxacin is 2.15 ng/mL. The mean peak plasma concentration after 500 mg of multiple oral doses of levofloxacin is 5.7 µg/mL (as per the package insert). The peak concentration after topical dosing 4-8 times daily is over 2000 folds lower than the oral dosing.

- The $t_{1/2}$ after oral dosing is the same (7 hours) as after topical dosing, which would predict accumulation of the drug in plasma with 4-8 times dosing per day.

- Levofloxacin undergoes limited metabolism, approximately 87% is excreted unchanged in urine and less than 5% as desmethyl and N-oxide metabolites upon oral administration. Considering the small fraction of the oral dose that is being administered topically, determination of metabolites of levofloxacin after topical administration is impractical and unnecessary. The sponsor has not determined the metabolite concentrations, which seems reasonable.

*Another Phase I study was carried out to determine the levofloxacin concentrations in the serum (*Japanese Study 95034*)*

Levofloxacin concentrations were determined following repeat administration of 0.3% in one eye and 0.5% levofloxacin solution with the preservative Benzalkonium chloride in the other eye. Subjects received a single dose on Day 1 and then q.i.d dosing for 2 weeks. In this study the levofloxacin concentrations were determined in the serum and were below the limit of quantitation (10 ng/mL) in all samples. The limit of quantitation is much higher in this study and as such does not lend any pertinent information for this application.

Like the other Fluoroquinolone antibacterial agents, are the levels of levofloxacin evaluated in human tears?

What is the significance of the concentration-time profile in the tears?

The sponsor has evaluated the levofloxacin concentrations in human tears. The results are described below. The relevance of this study in relation to efficacy is discussed under the Reviewer's Comment.

An open-label, single center trial of levofloxacin tear concentration following administration of 0.5% levofloxacin ophthalmic solution in healthy adult volunteers with asymptomatic eyes (Study 03-006)

One drop of 0.5% levolfloxacin ophthalmic solution (lot 81864) in each eye was administered to 30 healthy adult volunteers (20F & 10M, 18-65 years age, 12 Caucasian & 18 Hispanic). Subject demographics are attached in the Appendix on page 11. Each subject was assigned to one of the five groups; there were 6 subjects per group.

Tear Samples:

Tear samples were collected using a [redacted] from each group and each eye at predetermined time points up to 24 hours post dose (5, 10, 15 and 30 mins, 1, 2, 4, 6 and 24 hour). Only one sample was collected from each eye of each subject. Tear samples were collected from the various groups at the following time points.

Group I: 5 minutes (right eye) and 10 minutes (left eye)
Group II: 15 minutes (right eye) and 30 minutes (left eye)
Group III: 1 hour (right eye) and 2 hour (left eye)
Group IV: 4 hour (right eye) and 6 hour (left eye)
Group V: 24 hour (right & left eye)

Pharmacokinetic evaluation:

The mean tear concentration of levofloxacin is shown in the following Table. The individual subject data is attached in the Appendix on pages 12-13.

Time	Mean Concentration (µg/mL)	SD	Range (µg/mL)	90% Confidence Limits*
5 min	49.19	26.73		26.3-74.2
10 min	49.46	46.47		13.0-93.8
15 min	221.06	256.68		16.1-563.5
30 min	43.24	36.05		3.7-129.2
1 hr	34.89	11.11		24.3-46.2
2 hr	36.80	32.95		10.0-68.4
4 hr	17.04	15.13		1.9-43.9
6 hr	6.57	5.26		1.3-14.2
24 hr	1.37	1.44		-2.0-1.7

*CI provided from log transformed data, antilog values are provided.

Observations

- Levofloxacin was present in all tear samples collected up to 24 hours post dose.
- Peak concentrations of levofloxacin in the tears occurred at 15 minutes post-dose and concentrations declined thereafter, which is consistent with the kinetics of tear fluid.
- There is high inter-subject variability as indicated by the standard deviations.

Reviewer's Comment/Conclusion:

- The minimum inhibitory concentration (MIC90) for levofloxacin is 2 µg/mL. Although the sponsor claims that the levofloxacin concentration in the human tears were above or at the MIC up to 4 hours post dose, the scientific relevance of this has not been studied anywhere. In the literature too, researchers have studied the concentrations of other fluoroquinolones in the tears. The MIC can only be used as a reference concentration that would be desirable, the influence of concentrations below the MIC in tears have not been studied.

V. LABEL

Minor labeling changes have been made to the last line of the following label:

Pharmacokinetics:

/S/

Veneeta Tandon, Ph.D.
Pharmacokineticist
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Team Leader: E. Dennis Bashaw, Pharm. D. /S/

CC: NDA 21-199
HFD-550/Div File
HFD-550/CSO/Puglisi
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy