# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-571**

# CHEMISTRY REVIEW(S)

# NDA 21-571

## IQUIX®
## (levofloxacin ophthalmic solution) 1.5%

Santen Inc

Hossein S. Khorshidi
Division of Anti-Inflammatory/Analgesics & Ophthalmic
Drug Products
HFD-550

# Table of Contents



APPEARS THIS WAY
ON ORIGINAL

# Chemistry Review Data Sheet

1. NDA # **21-571**

2. REVIEW # 2

3. REVIEW DATE: February 20, 2003

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

None

**6. SUBMISSION(S) BEING REVIEWED:**

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 5/1/2003 |
| Amendment | 6/30/2003 |
| Amendment | 9/17/2003 |
| Amendment | 10/1/2003 |
| Amendment | 10/7/2003 |

7. NAME & ADDRESS OF APPLICANT:

Name: Santen Inc

APPEARS THIS WAY
ON ORIGINAL

Address: 555 Gateway Drive
Napa, California, USA 94558

Representative: Lisa Ann Suchar

Telephone: 707-256-2407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iquix® (levofloxacin ophthalmic solution), 1.5%
b) Non-Proprietary Name (USAN): levofloxacin ophthalmic solution
c) Code Name/# (138):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Corneal Ulcer

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1.5%
The proposed dosing regimen is [redacted]

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| — | II | Daiichi Pharmaceutical, Japan | Manufacturer of the drug substance | 1 | Adequate | July 15, 2003<br>October 2, 2003 | |
| — | III | — | [ ] | 3 | Adequate | | |
| — | III | — | [ ] | 3 | Adequate | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| NDA | 21-199 | Quixin®(levofloxacin ophthalmic solution) 0.5% |
| NDA | 20-634 | Levaquin® tablet |
| NDA | 20-635 | Levaquin® injection |
| IND | 58,997 | Levofloxacin ophthalmic solution, 1.5% |
| | | |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | | | |
| EES | Acceptable | 2/26/04 | Hossein Khorshidi |
| Pharm/Tox | | | |
| Biopharm | | | |
| LNC | | | |
| Methods Validation | Not Required | | Hossein khorshidi |
| OPDRA | | | |
| EA | Acceptable | 10/6/03 | Hossein Khorshidi |
| Microbiology | Approval | 9/24/03 | Bryan Riley |

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for NDA # 21-571

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommend for Approval.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(1). The proposed indication is for the [redacted]. The drug substance is licensed for ophthalmic use from Daiichi Pharmaceutical Co., in Japan. [redacted]. Santen has cross referenced approved NDAs 20-634 for Levaquin®tablets and Levaquin® injection in support of this application. The applicant has also cross-referenced Santen NDA's 21-199 for Quixin® (levofloxacin ophthalmic solution, 0.5%) approved on 18 August 2000 for the treatment of bacterial conjunctivitis.

### A. Description of the Drug Product(s) and Drug Substance(s)

*Drug Substance:*

Levofloxacin (LVFX) is the L-isomer of ofloxacin. It has been demonstrated that most of the antimicrobial activity of ofloxacin is associated with LVFX enantiomer. [redacted]. Levofloxacin hemihydrate has been used to formulate a previously approved Santen product, Quixin® (levofloxacin ophthalmic solution, 0.5%). Daiichi Pharmaceutical (Japan) is the manufacturer of the drug substance . The most recent inspection of the firm was conducted on November, 1998. A new inspection request was initiated and the result is still pending. Daiichi's DMF [redacted] has been reviewed and found to be adequate.

*Drug product:*

The drug product is a sterile ophthalmic solution containing 1.5% of the active ingredient levofloxaxin hemihydrate. The inactive ingredients include glycerin, hydrochloridric acid, sodium hydroxide and purified water. No preservative is used in this formulation. It has been demonstrated that the use of glycerin —

The bulk solution for the registration/commercial batches were — scale (— , in total). The manufacturing process consists of ; — Appropriate in-process tests/controls for the appearance, identity, assay, related substances, osmolality, pH, — sterility and preservative effectiveness are included.

The drug product specification was similar to the approved NDA 21-199 with a slight exception on the impurities and osmolality's acceptance criteria. All analytical procedures and their validation were similar to those used for the approved NDA 21-199. Therefore, the validation of the analytical procedures by the FDA's laboratories will not be required for this NDA.

— are proposed for the marketing of this product; — — 5 ml fill/5cc LDPE bottles. The container/closure components are the same as those used for the approved NDA 21-199, supplement 003. The three-piece container/closure system consists of a white LDPE bottle, a — dropper tip and a tan HDPE cap. All related DMFs have been found adequate to support the current NDA. Results of the — ; studies for the samples stored at long term and accelerated stability conditions are provided. The results were satisfactory.

For the 5ml fill/5cc bottles, — of long term (25°C ±2°C/40%±5%RH) and — — , of accelerated stability data (40°C ±2°C/≤25%RH) or — are provided. —

**B. Description of How the Drug Product is Intended to be Used**

Iquix® (levofloaxcin ophthalmic solution, 1.5) is used topically. The proposed dosing regimen is —

— The label storage temperate of 15°C-25 °C (59° - 77° F) is proposed for this drug. Based on stability data, the proposed expiration-dating periods of — 24 months for the 5 ml fill/5cc LDPE bottles are acceptable.

### C. Basis for Approvability or Not-Approval Recommendation

NDA 21-571 was not approved in review No.1 due to pending inspection result of Daiichi Pharmaceuticals. Inspection of Daiichi Pharmaceuticals is completed with overall acceptable recommendation by the office of compliance on 2/26/04. Therefore, from CMC standpoint, this NDA is approved.

## III Administrative

### A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

### B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

---

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

[redacted]

Profile: CSN OAI Status: NONE

| Milestone Name | Date | Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 10-JUN-2003 | | | | KHORSHIDIH |
| SUBMITTED TO DO | 10-JUN-2003 | GMP | | | DAMBROGIOJ |
| ASSIGNED INSPECTION T | 23-JUN-2003 | GMP | | | DAMBROGIOJ |
| INSPECTION SCHEDULED | 14-JAN-2004 | | 24-FEB-2004 | | IRIVERA |
| INSPECTION PERFORMED | 24-FEB-2004 | | 24-FEB-2004 | | ADAMSS |
| OC RECOMMENDATION | 26-FEB-2004 | | | ACCEPTABLE | ADAMSS |
| DO RECOMMENDATION | 26-FEB-2004 | | | DISTRICT RECOMMENDATION ACCEPTABLE | ADAMSS |

INSPECTION

---

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

---

/s/

---

Hossein Khorshidih
2/26/04 12:51:40 PM
CHEMIST

Linda Ng
2/26/04 12:55:45 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

# NDA 21-571

**IQUIX®**
**(levofloxacin ophthalmic solution) 1.5%**

**Santen Inc**

**Hossein S. Khorshidi**
**Division of Anti-Inflammatory/Analgesics & Ophthalmic Drug Products**
**HFD-550**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA # **21-571**

2. REVIEW # 1

3. REVIEW DATE: October 7, 2003

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

None

**6. SUBMISSION(S) BEING REVIEWED:**

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 5/1/2003 |
| Amendment | 6/30/2003 |
| Amendment | 9/17/2003 |
| Amendment | 10/1/2003 |
| Amendment | 10/7/2003 |

7. NAME & ADDRESS OF APPLICANT:

Name: Santen Inc

Address: 555 Gateway Drive
Napa, California, USA 94558

Representative: Lisa Ann Suchar

Telephone: 707-256-2407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iquix® (levofloxacin ophthalmic solution), 1.5%
b) Non-Proprietary Name (USAN): levofloxacin ophthalmic solution
c) Code Name/# (138):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Corneal Ulcer

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1.5%
The proposed dosing regimen is

13. ROUTE OF ADMINISTRATION: Topical

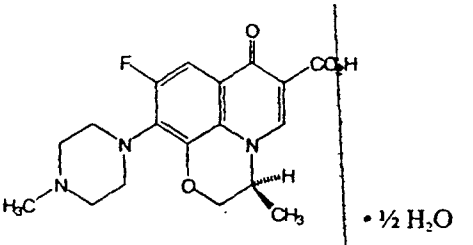
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet




| | |
|---|---|
| **Molecular Formula** | $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2} H_2O$ |
| **Molecular Weight** | 370.38 |
| **Stereoisomerism** | L-isomer of ofloxacin |

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| — | II | Daiichi Pharmaceutical, Japan | Manufacturer of the drug substance | 1 | Adequate | July 15, 2003<br>October 2, 2003 | |
| — | III | — | / | 3 | Adequate | | |
| | III | — | / | 3 | Adequate | | |
| L | | | | ⊥ | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| NDA | 21-199 | Quixin®(levofloxacin ophthalmic solution) 0.5% |
| NDA | 20-634 | Levaquin® tablet |
| NDA | 20-635 | Levaquin® injection |
| IND | 58,997 | Levofloxacin ophthalmic solution, 1.5% |
| | | |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | | | |
| EES | Pending | As of 11/10/03 | Hossein Khorshidi |
| Pharm/Tox | | | |
| Biopharm | | | |
| LNC | | | |
| Methods Validation | Not Required | | Hossein khorshidi |
| OPDRA | | | |
| EA | Acceptable | 10/6/03 | Hossein Khorshidi |
| Microbiology | Approval | 9/24/03 | Bryan Riley |

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for NDA # 21-571

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommend for Not Approval pending satisfactory inspection result of Daiichi Pharmaceuticals (Japan).

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(1). The proposed indication is for the treatment of corneal ulcer in adults and children —— of age and older. The drug substance is licensed for ophthalmic use from Daiichi Pharmaceutical Co., in Japan.

—————— —————— Santen has cross referenced approved NDAs 20-634 for Levaquin®tablets and Levaquin® injection in support of this application. The applicant has also cross-referenced Santen NDA's 21-199 for Quixin® (levofloxacin ophthalmic solution, 0.5%) approved on 18 August 2000 for the treatment of bacterial conjunctivitis.

### A. Description of the Drug Product(s) and Drug Substance(s)

*Drug Substance:*

Levofloxacin (LVFX) is the L-isomer of ofloxacin. It has been demonstrated that most of the antimicrobial activity of ofloxacin is associated with LVFX enantiomer. ——

—————— Levofloxacin hemihydrate has been used to formulate a previously approved Santen product, Quixin® (levofloxacin ophthalmic solution, 0.5%). Daiichi Pharmaceutical (Japan) is the manufacturer of the drug substance . The most recent inspection of the firm was conducted on November, 1998. A new inspection request was initiated and the result is still pending. Daiichi's DMF ——— has been reviewed and found to be adequate.

*Drug product:*

The drug product is a sterile ophthalmic solution containing 1.5% of the active ingredient levofloxaxin hemihydrate. The inactive ingredients include glycerin, hydrochloridric acid, sodium hydroxide and purified water. No preservative is used in this formulation. It has been demonstrated that the use of glycerin

The bulk solution for the registration/commercial batches were scale ( in total). The manufacturing process Appropriate in-process tests/controls for the appearance, identity, assay, related substances, osmolality, pH, sterility and preservative effectiveness are included.

The drug product specification was similar to the approved NDA 21-199 with a slight exception on the impurities and osmolality's acceptance criteria. All analytical procedures and their validation were similar to those used for the approved NDA 21-199. Therefore, the validation of the analytical procedures by the FDA's laboratories will not be required for this NDA.

are proposed for the marketing of this product; d 5 ml fill/5cc LDPE bottles. The container/closure components are the same as those used for the approved NDA 21-199, supplement 003. The three-piece container/closure system consists of a white LDPE bottle, a dropper tip and a tan HDPE cap. All related DMFs have been found adequate to support the current NDA. Results of the studies for the samples stored at long term and accelerated stability conditions are provided. The results were satisfactory.

For the 5ml fill/5cc bottles. of long term (25°C ±2°C/40%±5%RH) and of accelerated stability data (40°C ±2°C/≤25%RH) on are provided

**B. Description of How the Drug Product is Intended to be Used**

Iquix® (levofloaxcin ophthalmic solution, 1.5) is used topically. The proposed dosing regimen is

The label storage temperate of 15°C-25 °C (59° - 77° F) is proposed for this drug. Based on stability data, the proposed expiration-dating periods of 24 months for the 5 ml fill/5cc LDPE bottles are acceptable.

### C. Basis for Approvability or Not-Approval Recommendation

In conclusion of this chemistry review, the following recommendation were made.

*Revision to the drug product specification:*

The applicant was asked to revise the drug product specification as following: NMT —, for———————, NMT—— for total impurities and ———— ———— for the osmolality test. Santen accepted the Agency's proposal.

In general, the applicant has provided adequate chemistry information to support the approval of this NDA . However, the inspection of Daiichi Pharmaceuticals (manufacturer of the drug substance) has not been performed yet. Therefore, from CMC standpoint, this application can not be approved at this time.

## III Administrative

### A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

### B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

APPEARS THIS WAY
ON ORIGINAL

37 Page(s) Withheld

---

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

---

/s/

---

Hossein Khorshidih
12/2/03 01:36:36 PM
CHEMIST

Linda Ng
12/2/03 06:00:17 PM
CHEMIST