

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-199

CORRESPONDENCE



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

28 February 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

**RE: NDA 21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Original NDA**

Dear Dr. Chambers:

Pursuant to 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.50, Santen hereby submits a New Drug Application (NDA) for 0.5% Levofloxacin Ophthalmic Solution (QUIXIN™).

The proposed indication for this product is for the treatment of bacterial conjunctivitis, in both adults and children 1 year of age and older. The proposed dosing regimen is q 2h up to 8x/day on Days 1 and 2, and q 4h up to 4x/day on Days 3 through 5.

The compound was licensed from Daiichi Pharmaceuticals, Inc. (Daiichi), who manufactures and markets systemic levofloxacin formulations ex-US for the treatment of various systemic infections. The Robert Wood Johnson Pharmaceutical Research Institute (RW Johnson), also under license from Daiichi, markets oral and intravenous formulations of levofloxacin in the US. Santen has permission to cross-reference these systemic NDAs (20-634 and 20-635). A letter of authorization is located in the General Information section and excerpts from their NDA summaries are located in the appropriate technical sections.

The primary clinical support for this NDA consists of six clinical studies conducted in the US under [redacted]. Pivotal safety and efficacy data is based on two adequate and well-controlled studies designed in conjunction with the Agency.

Study 03-003 evaluated the safety and efficacy 0.5% levofloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution in 200 patients one year of age and older. Study 03-004 evaluated the safety and efficacy of 0.5% levofloxacin ophthalmic solution versus placebo in 100 patients 2 years of age and older. In both studies, patients dosed every 2 hours while awake up to 8x/day on Days 1 and 2, and then every 4 hours while awake up to 4x/day on Days 3 through 5.

Supportive information includes data generated by Santen Pharmaceutical Co., Ltd. with a 0.5% levofloxacin ophthalmic solution formulated without the preservative, benzalkonium chloride and postmarketing information on systemic formulations. Over 500 subjects were evaluated in the Japanese ophthalmic clinical studies and the NDA was approved January 2000 by the Japanese Ministry of Health.

In lieu of a pre-NDA meeting, a teleconference was held with Ms. Lori Gorski, Ms. Joanne Holmes, and Dr. William Boyd to discuss the NDA presentation and format (18 August 1999). Based on that teleconference, the NDA is presented as follows:

- The NDA review and archival copies are submitted in paper format. An electronic copy of the NDA in Portable Document Format (pdf using CoreDossier®) will be forwarded to the Agency to facilitate review.
- Twenty (20) paper copies of the NDA summary and electronic copies (MS Word '97 version) of the major technical sections (Sections 4, 5, 6, 7, 8/10/11), annotated labeling, draft package insert and the NDA summary will be sent directly to Ms. Gorski under separate cover.
- A copy of the User Fee Statement (User Fee ID 3818) and other necessary forms and certifications have been placed under independent tabs after the cover letter and application form.
- Sterilization validation information is included in the Chemistry, Manufacturing, and Controls section (red jacket) and the Microbiology section (white jacket) of the NDA.
- Methods validation information is included in the Chemistry, Manufacturing and Controls section of the NDA.
- Three complete review copies of the NDA Clinical Sections (Sections 8 to 12) are provided. The annotated case report forms and SAS transport files are located in Section 12.

User fee funds were sent directly to Mellon Bank on 7 January 2000 and a certified field copy has been submitted to our District Office (San Francisco). All sites involved in the manufacturing, testing, and release of product are preapproval inspection ready.

Santen would like to thank you and the other Division representatives for your advice and recommendations throughout the development of this product. We are looking forward to continuing to work closely with you during the approval process.

If there are any questions regarding this application, please contact:

Elaine Alambra (707) 256-2456
Manager, Regulatory Affairs

Michelle Carpenter (707) 256-2453
Director, Regulatory Affairs

Maggie Timms (707) 256-2451
VP, Regulatory Affairs

Sincerely,



Michelle Carpenter
Director, Regulatory Affairs

cc: Archival Copy
Review Copy

NDA 21-199

MAR 23 2000

Santen Incorporated
Attention: Margaret Reents Timms
Vice President, Regulatory Affairs
555 Gateway Drive
Napa, CA 94558

Dear Ms. Reents Timms:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Quixin (levofloxacin hemihydrate ophthalmic solution) Ophthalmic Solution, 0.5%

Therapeutic Classification: Priority (P)

Date of Application: February 28, 2000

Date of Receipt: March 1, 2000

Our Reference Number: NDA 21-199

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 30, 2000, in accordance with 21 CFR 314.101(a).

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632).

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

/s/

3-23-00

Leslie Vaccari
Acting Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V, HFD-550
Center for Drug Evaluation and Research

Santen

NTEN INCORPORATED

Gateway Drive
Irvine, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

NE ORIG AMENDMENT

12 April 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
ATTN: DOCUMENT CONTROL
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850

RE: RESPONSE TO FDA REQUEST FOR ADDITIONAL CLINICAL INFORMATION
NDA 21-199: Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 001

Dear Dr. Chambers:

This amendment is in response to the Food and Drug Administration's request, dated 31 March 2000, for electronic copies of the protocols for Studies 03-003 and 03-004. Original protocols for Studies 03-003 and 03-004 in MS Word/95 v. 6.0 are provided in the attached diskette.

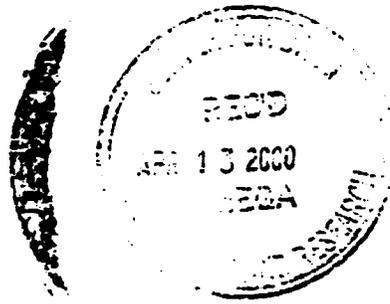
We hope you find the information provided satisfactory. If you have any questions, or need additional information, please contact me at (707) 256-2456.

Sincerely,

Elaine Alambra

Elaine Alambra
Manager, Regulatory Affairs

cc: Original: 2 copies



ORIGINAL



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755



21 April 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

NDA ORIG AMENDMENT

B2

**RE: NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Response to FDA Request for Additional Clinical/Statistical Information
Amendment 002**

Dear Dr. Chambers:

This amendment is in response to the Dr. Laura Lu's facsimile dated 31 March 2000 –
Clinical/Statistical request for additional information on Studies 03-003 and 03-004.

FDA request (1): Word documents for the original protocol.

**Santen response: Protocols for Studies 03-003 and 03-004 in Word format were provided in
NDA 21-199 A.001 submitted on 12 April 2000.**

**FDA request (2): A by-patient SAS dataset for each study including the patient number,
treatment code, investigator, demographic variables, reason for
terminating study, all primary and secondary efficacy variables at each
period and endpoint (by last-observation-carried-forward method), and
an indicator for Per-Protocol population. The formats for characteristic
variables such as investigator site, treatment, gender, race, and reasons for
terminating study should be provided.**

DUPLICATE

Santen response: A CD containing the requested SAS datasets for Studies 03-003 and 03-004 is enclosed as Attachment 1. Also included in the CD are the Data Definition Tables in rich text format (rtf) describing the characteristic variables of the datasets.

The original analysis datasets were derived from the database using methodology outlined in the Statistical Analysis Plan (SAP). These data were then transposed to meet FDA requested specifications. Two datasets were generated for each protocol: one for the intent-to-treat population and another for the per-protocol population. Along with the format catalog, these datasets were combined into SAS transport files. The following files are provided in the attached CD:

S03003.xpt - SAS transport file containing the two analysis datasets for 03-003.

Format03.xpt - SAS transport file containing format catalog for 03-003.

Defin003.rtf - Data definition report for 03-003 files.

S03004.xpt - SAS transport file containing the two analysis datasets for 03-004.

Format04.xpt - SAS transport file containing format catalog for 03-004.

Defin004.rtf - Data definition report for 03-004 files.

The S03003.xpt and S03004.xpt files were generated using PROC COPY. The Format03.xpt and Format04.xpt files were generated using PROC CPORT.

Analysis dataset specifications for Santen protocols 03-003 and 03-004.

a. Period Determination

For efficacy data, period is defined as Interim (Day 3- day 5), Final (Day 6 – day 10) and Endpoint. Endpoint is defined as the last evaluable period by using last-observation-carried-forward method. The 'Best Day' for the Interim period and Final period is Day 3 and Day 7 respectively. If two observations from one patient fell within one period, the observation closest to the 'Best Day' for that period was chosen. If two observations were equally close to the 'Best Day', the observation with the longer length of therapy was chosen.

b. Intent-to-Treat Population and Per-Protocol Population

The intent-to-treat population included all the patients who took at least one dose of study medication and had at least one post baseline data.

The per-protocol data set excluded all patients who were both clinically and microbially negative at baseline. Patients with other significant protocol violations (such as: disallowed medication, clinical entry criteria not met) were also excluded from the per-protocol data set.

FDA request (3): A summary table for each study for patient disposition for both Intent-to-Treat and Per-Protocol population including reasons for discontinuation such as lack of efficacy, adverse events, and lost-to-follow-up.

Santen response: See Attachment 2.

FDA comment (4): Ninety-five percent (95%) confidence intervals for the difference in clinical success and clinical cure between treatment arms weighted by size of study centers.

Santen response: See Attachment 3.

We hope you find the information satisfactory. If you have any questions, please call me or Michelle Carpenter, Director of Regulatory Affairs at 707-256-2456.

Sincerely,

Elaine Alambra

Elaine Alambra
Manager, Regulatory Affairs

cc: Original; 2 copies
Dr. L. Lu (FDA Statistician)
Mr. M. Puglisi (FDA Project Manager)

Santen

SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

NDA DRUG AMENDMENT



12 May, 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

BC

RE: RESPONSE TO 05/02/00 CHEMISTRY QUESTIONS
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 003

Dear Dr. Chambers:

This is a partial response to Dr. Khorshidi's questions of May 2, 2000. In a phone conversation with him on May 10th, it was explained that a total response would not be available until next week. Dr. Khorshidi said he would appreciate a response to those items we had answers to now. We have provided complete responses to questions 1, 3, 4, and 5 and partial response to question 7. We have also addressed in this response Dr. Khorshidi's request that the test methods be in the same order as listed on the specifications (Attachment 2). For ease of review, the questions are in bold followed by Santen's responses.

- 1. As per your commitment, a complete process validation and master batch record for [] batch size should be provided for review purpose as soon as possible.**

In the event that scale-up occurred during the NDA review process Santen considered it our obligation to report this activity to the Agency. However, due to summer plant shut down, the [] process validation lots cannot be made before August. This timeframe makes it unlikely that the data will be available before the Agency's NDA action date.

According to November 1999 FDA guidance on changes to an approved NDA, scale-up requiring less than a 50% increase in total processing time may be submitted as a change being effected supplement. Therefore this scale-up will be submitted as a change being effected, post-approval. All references to scale-up are deleted from the NDA at this time.

DUPLICATE

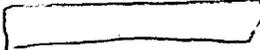
- 2. Total manufacturing time (including allowed filtration) and also storage time (before filling) should be identified in the master batch records.**

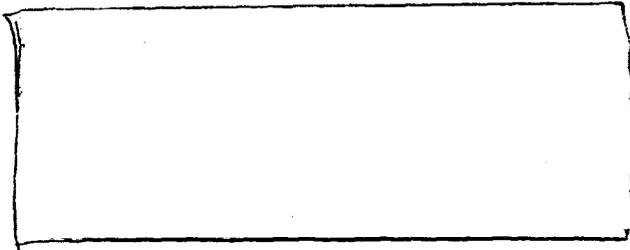
We are currently working on obtaining data in order to respond to this question.

- 3. In drug product release specifications, the proposed acceptance criteria for osmolality, BAK assay, D -ofloxacin and Related substances are high and need to be tightened. Based on actual data, the following acceptance criteria for above test parameters are proposed.**

Osmolality: 240-340 mOsm/Kg

BAK assay: 85 % - 110 %

D-Ofloxacin: 



We do not understand your question regarding release specifications. The NDA contains only the regulatory (shelf-life) specifications, provided in Volume 2, pg. 23 & 106 of the NDA. Could you please clarify.

- 4. Please provide sample HPLC chromatograms of long term extractables studies (at 18 months). This includes chromatograms of all labeled and unlabeled drug products and placebo control. Also comment whether the same HPLC method is used for assay, related substances and extractable studies or not.**

As requested, sample chromatograms are provided in the Attachment 1 showing HPLC profiles for the following:

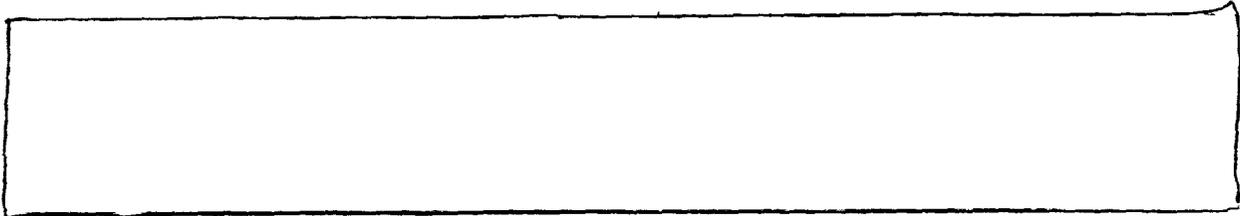
1. BAK standard
2. Drug Product Lot 73821 Labeled
3. Drug Product Lot 73821 Unlabeled
4. Placebo Lot 73740 Labeled
5. Placebo Lot 73740 Unlabeled

Different HPLC methods are used for levofloxacin assay, related substances, and extractables. Each of the methods is provided on the following pages of the NDA:

Levofloxacin assay: Volume 2, pg. 222

Related substances: Volume 2, pg. 225

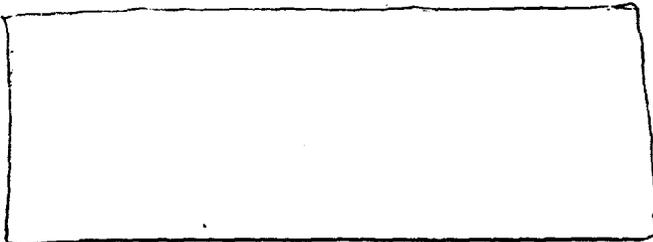
Extractables: Volume 3, pg. 64



5. Initial [redacted] testing should be included in all stability protocols for the 5.0 mL fill bottles and data should be submitted (this includes long term, intermediate and accelerated stability conditions).

Instructions for [redacted] testing were inadvertently omitted from the 5.0 mL stability protocols. However, the data were included in the corresponding stability reports. Subsequent protocols will contain explicit instructions for [redacted] testing.

6. All known individual impurities should be listed with acceptance criteria in the stability specifications. Based on actual data, we propose the following acceptance criteria:



We are currently working on obtaining data in order to respond to this question.

7. In drug product stability specifications, the proposed acceptance criteria for Osmolality, BAK assay, D-Ofloxacin are high and need to be tightened. Based on actual data, the following acceptance criteria for the above tests are proposed:

Osmolality: 240-340 mOsm/Kg

BAK Assay: 85-110 %

D-Ofloxacin:

Osmolality: We agree with the Agency and will change the product stability specifications to the following:

Osmolality: 240 – 340 mOsm/Kg

BAK Assay: Preservative efficacy studies of BAK have demonstrated that the product is adequately preserved under this range of BAK levels. Please refer to the BAK which showed preservative efficacy down to (Volume 07, pg. 131)

D-Ofloxacin: *We are currently working on obtaining data in order to respond to this question.*

Also, as per Dr. Khorshidi's request (phone contact dated 05/10/99), for test methods to be re-ordered, the test methods are now listed in the order of the specifications. Attached is the actual English translation of the Finnish Document Revision Sheet (revision date 17/5/00), for the 0.5% Levofloxacin Ophthalmic Solution test methods (Attachment 2).

APPEARS THIS WAY
ORIGINAL

If there are any questions regarding this response, please contact me at 707-256-2451 or Michelle Carpenter at 707-256-2453. We look forward to hearing from you.

Sincerely,



Margaret Reents Timms
Vice-President, Regulatory Affairs and Project Management

cc: Archival Copy
Review Copy
Mr. Mike Puglisi, Project Manager

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755



17 May, 2000

NDA ORIG AMENDMENT

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

BC

RE: Response to Agency Request for Chemistry, Manufacturing, and Controls Information
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 004

Dear Dr. Chambers:

Per the request of Dr. Khorshidi, this amendment contains the drug substance supplier's (Daiichi Pharmaceutical Co., Ltd.) revised drug substance specifications. These specifications were revised by Daiichi at the request of Dr. Khorshidi and their US Drug Master File has been accordingly updated.

The drug substance is released by Santen based on Daiichi's Certificate of Analysis and an additional appearance and identity test.

If there are any questions regarding this amendment please contact me at (707) 256-2453.

Sincerely,

Michelle A. Carpenter

Michelle Carpenter
Director, Regulatory Affairs

DUPLICATE

cc: Original, 2 copies
Mr. Mike Puglisi, Project Manager



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

AMENDMENT

BC



18 May, 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

RE: RESPONSE TO 05/02/00 CHEMISTRY QUESTIONS
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 005

Dear Dr. Chambers:

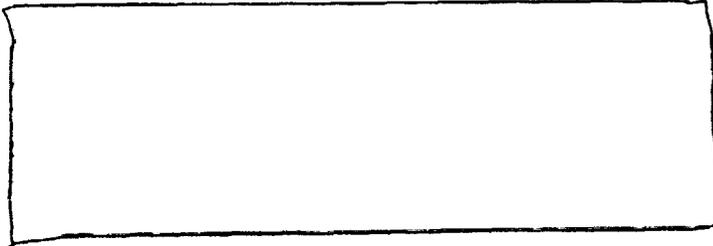
This amendment completes Santen's responses to the written Chemistry, Manufacturing and Controls questions posed by Dr. Khorshidi as of this date. Partial responses to the questions received on May 2 were submitted to the Agency on May 12 (amendment 003). A full copy of the questions are appended to Santen's responses for ease of review.

- 2. Total manufacturing time (including allowed filtration) and also storage time (before filling) should be identified in the master batch records.**

As per the Agency request, the total manufacturing time will be identified in the master batch records. The total manufacturing time is up to and the storage time after filtration and prior to filling is up to .

DUPLICATE

6. All known individual impurities should be listed with acceptance criteria in the stability specifications. Based on actual data, we propose the following acceptance criteria:



Based on our understanding of degradation pathways for levofloxacin coupled with our limited manufacturing experience of only 6 lots with 5mL fill and 3 lots of 2.5mL fill, we propose tightening our current end-of-shelf specification as follows:

	Original NDA specifications	Amended NDA specifications

*With a commitment to identify any single impurity present at >0.1%

As more data are generated, we will work with the Agency to refine these specifications as appropriate.

APPEARS THIS WAY
ON ORIGINAL

7. In drug product stability specifications, the proposed acceptance criteria for Osmolality, BAK assay, D-Ofloxacin are high and need to be tightened. Based on actual data, the following acceptance criteria for the above tests are proposed:

Osmolality: 240-340 mOsm/Kg

BAK Assay: 85-110 %

D-Ofloxacin:

As per the Agency recommendation the specification for D-Ofloxacin will be tightened from NMT to NMT Responses regarding osmolality and BAK specifications were provided in amendment 003.

If there are any questions regarding this response, please contact me at 707-256-2453 or Ms. Elaine Alambra at 707256-2451. Per our agreement with Dr. Khorshidi, more comprehensive explanations of the USP test methods used for drug product testing will be submitted to the NDA in the next several days.

Sincerely,



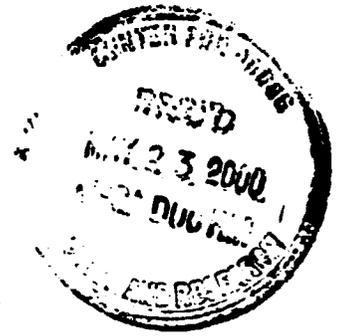
Michelle A. Carpenter,
Director, Regulatory Affairs

cc: Original, 2 copies
Mr. Mike Puglisi, Project Manager



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755



19 May, 2000

NDA ORIG AMENDMENT

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

BC

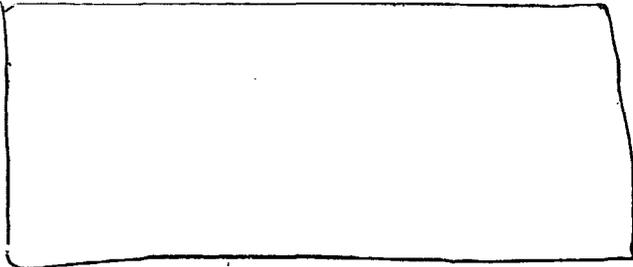
RE: RESPONSE TO CHEMISTRY QUESTIONS
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 006

Dear Dr. Chambers:

In this amendment we complete our responses to the written and verbal requests for chemistry information for NDA 21-199 as of this date. Santen would like to thank Dr. Khorshidi for his rapid review.

After obtaining clarification regarding question 3 (correspondence dated May 2, 2000), the drug product release specifications will be modified as follows:

Osmolality: 240-340 mOsm/kg
BAK assay: 80%-110%
D-Ofloxacin:



DUPLICATE

These specifications will continue to be evaluated as more data are generated.

Per agreement with Dr. Khorshidi (telephone contact with Margaret Timms, dated 05/12/00), a comprehensive description of the pharmacopoeial methods used for drug product testing are also provided in this amendment.

If there are any questions regarding the information in this amendment, please contact me at 707-256-2453 or Ms. Elaine Alambra at 707-256-2456

Sincerely,



Michelle A. Carpenter,
Director, Regulatory Affairs

cc: Original, 2 copies
Mr. Mike Puglisi, Project Manager

APPEARS THIS WAY
ON ORIGINAL



DUPLICATE

SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

ORIG AMENDMENT

BB



31 May, 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

RE: **RESPONSE TO BIOPHARMACEUTICAL QUESTION**
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 007

Dear Dr. Chambers:

This amendment is Santen's response to the request for biopharmaceutical information regarding NDA 21-199. We were asked to provide data on the long-term stability of levofloxacin in human tears on [redacted] for the duration that it was stored prior to analysis of the samples (Attachment 1).

A study was conducted by a contract laboratory, [redacted], to determine the stability of levofloxacin in human tears on [redacted]. Attached is an *unaudited, draft* addendum to the Sample Analysis Report for Study Protocol No. 03-006: *Determination of Levofloxacin in Human Tears by High Performance Liquid Chromatography*. The addendum summarizes the outcome of this stability investigation. The original Sample Analysis Report, located in Section 6, Volume 14 of the NDA, is incorporated into Appendix 17.1.10 of final Clinical Study Report for Protocol 03-006.

In summary, the results reveal that levofloxacin in human tears on [redacted] was stable at approximately [redacted] for a period of at least 11 weeks. The clinical samples were analyzed within this 11-week period (approximately 30 days). The *draft* report is attached along with a copy of the study calculation output (Attachment 2).

0100001

If there are any questions regarding the information in this amendment, please contact me at 707-256-2453.

Sincerely,

Michelle A. Carpenter (JAS)

Michelle A. Carpenter,
Director, Regulatory Affairs

cc: Original, 2 copies
Mr. Mike Puglisi, Project Manager

APPROVED THIS WAY
ON ORIGINAL

APPROVED THIS WAY
ON ORIGINAL



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

AMENDMENT

BC



09 June, 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

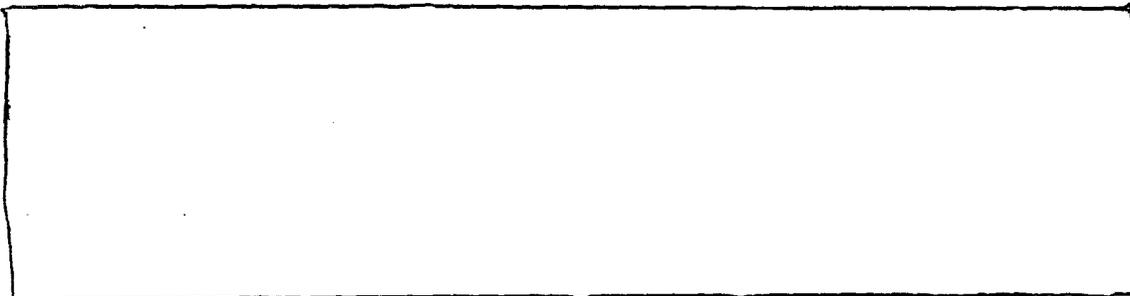
**RE: Response to 06/06/00 Chemistry Questions and Stability Data Update
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 008**

Dear Dr. Chambers:

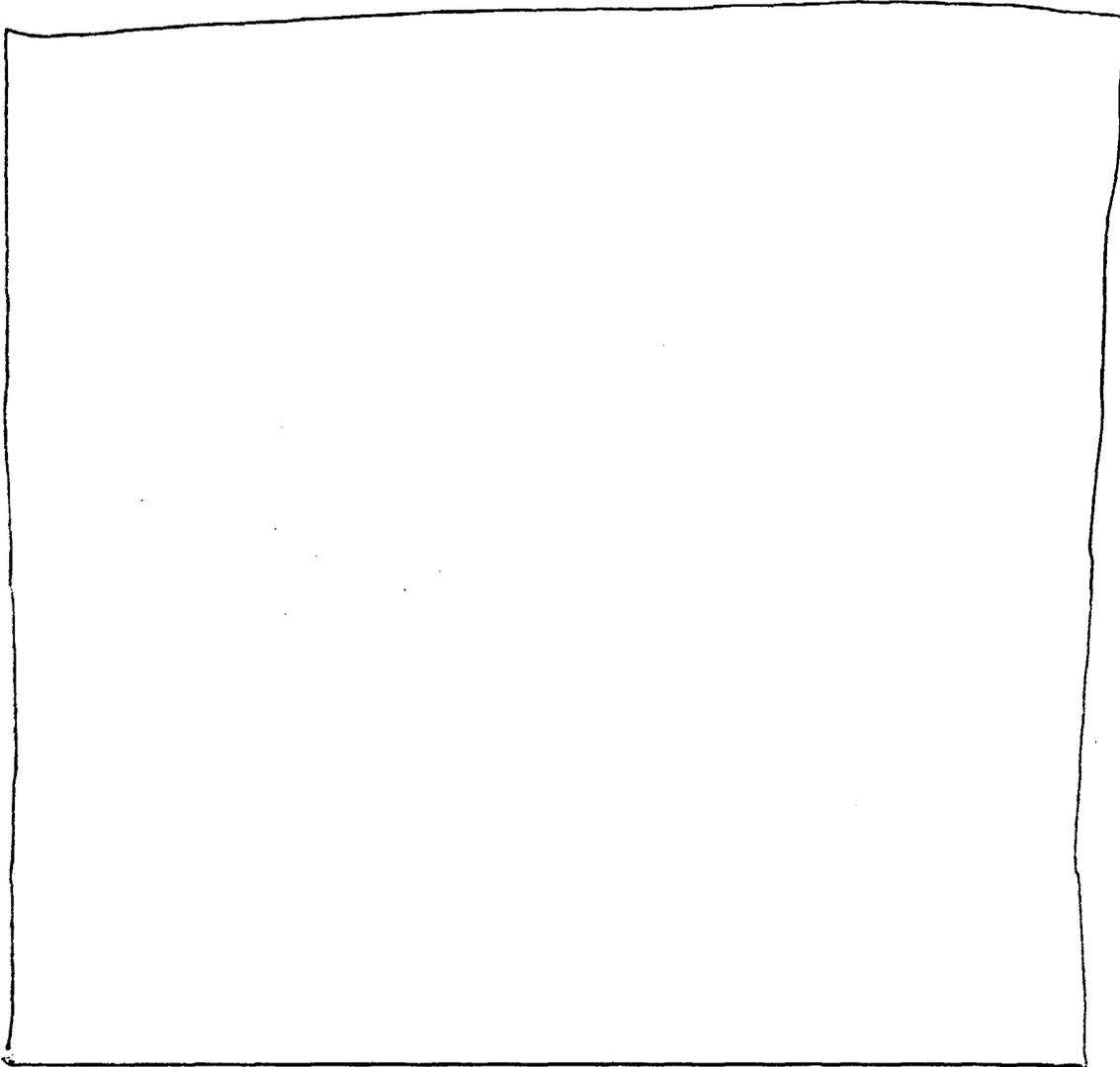
This amendment contains Santen's responses to the written Chemistry, Manufacturing and Controls questions posed by Dr. Khorshidi on June 6th. Also, as per Dr. Khorshidi's request, updated stability data tables are provided (Attachment 1). This includes the 18-month data for the 5mL and 2.5mL fill registration lots - 81525, 81863, & 81864 (5mL fill); 81905, 81906, & 81924 (2.5mL fill). For the three supportive lots (73821, 73822, & 80108), 24-month data is provided.

Following are Santen's responses to the Agency's Chemistry questions, which appear in bold:

- 1. In validation reports for HPLC assay, related substances and levofloxacin enantiomers (Vol 7.0, pages 168, 199 and 264), please identify the kind of "diluent(s)" used for the preparation of standard solution and sample. Moreover, specify the final concentration of the sample solution in the validation report for HPLC assay at Vol. 7.0, pages 168 of NDA submission.**



DUPLICATE

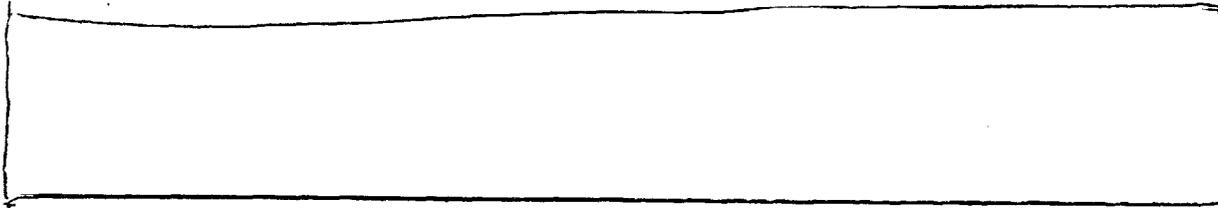


2. In Vol. 7.0, page 199 of NDA submission (where you discussed the validation of HPLC method for related substances), two different values, [redacted] have been identified for resolution (R) between the two adjacent peaks. Please specify which of these values is the correct one? Moreover, and for better resolution, we recommend that the resolution (R) between the two adjacent peaks to be set at [redacted]

Both resolution values are correct. A resolution of [redacted] which agrees with the Agency's recommendation, was assigned to any peak eluting adjacent to the main levofloxacin peak. A resolution of [redacted] was assigned to levofloxacin related substances or degradation peaks eluting adjacent to each other. These values were set as part of the acceptance criteria indicated in the "Specificity" section of the related substance HPLC validation protocol (Validation Plan No. 3070S003) and discussed

***This page of the document
contains confidential
information that will not
be included in the
redacted portion of the
document for the public to
obtain.***

in the "Specificity" section of the related substance validation report (Vol. 7.0, page 200).



4. Provide mock-up representations in actual color and size for all to be marketed bottles and cartons.

Mock-up representations in actual color and size for all to be marketed bottles and cartons are provided as Attachment 2.

If there are any questions regarding this response, please contact me at 707-256-2453 or Margaret Timms at 707 256-2451.

Sincerely,

A handwritten signature in cursive script that reads "Michelle A. Carpenter".

Michelle A. Carpenter,
Director, Regulatory Affairs

cc: Original, 2 copies
Mr. Mike Puglisi, Project Manager



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755



12 June, 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

NDA ORIG AMENDMENT
BC

RE: Registration Stability Data (Upright Orientation)
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Amendment 009

Dear Dr. Chambers:

This amendment contains the stability data tables (upright orientation) for the registration lots 81525, 81863 and 81864 (5mL fill) and; 81905, 81906 and 81924 (2.5mL) which were requested by Dr. Khorshidi.

If there are any questions regarding this response, please contact me at 707-256-2453 or Margaret Timms at 707 256-2451.

Sincerely,

Michelle A. Carpenter,
Director, Regulatory Affairs

cc: Original, 2 copies
Mr. Mike Puglisi, Project Manager

DUPLICATE



SANTEN INCORPORATED

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21 June 2000

NDA ORIG AMENDMENT

Shawn Khorshidi, Ph.D.
Chemistry Reviewer
Food and Drug Administration
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

BC

**RE: NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Methods Validation Package / Drug Sample Listing
Amendment 010**

Dear Dr. Khorshidi:

This amendment contains the methods validation information requested by you. As per your request (telephone contact dated 06/16/00), the following information is attached. A table of contents for this amendment follows this letter for your convenience.

1. Attachment 1: NDA Methods Validation Summary Section (NDA pg. 02-104 to 02-108). This section of the NDA provided a list of the drug product, drug substance and reference standard samples set aside for analysis by the Agency laboratories, as per 21CFR 314.50(e). The sample listing of the related substances and BAK is also provided.
2. Attachment 2: Drug Product Test Methods (02BC728450K, version 1.1). provides description of the test methods. The test methods document was revised such that the test methods are now listed in the order requested by the FDA. Additionally, Amendment 6, dated May 19th, 2000 provides detailed description of the methodology for the pharmacopoeial test methods, as requested by FDA.
3. Attachment 3: Drug Substance Test Method (03H5034694K). (NDA pg. 07-162 to 07-164) which includes the routine testing. We have completed the vendor qualification and full testing of drug substance is done once a year. For detailed description of levofloxacin, please refer to the Daiichi DMF for which we have permission to cross-reference.

ORIGINAL

4. Attachment 4: Assay validation reports for levofloxacin (NDA pg. 07-165 to 07-194), levofloxacin related substances (NDA pg. 07-195 to 07-237), BAK (NDA pg. 07-238 to 07-260) and levofloxacin enantiomers (NDA pg. 07-261 to 07-287), are provided. Additionally, Amendment 8, dated June 9th, 2000 which provides clarification regarding these assays is included.
5. Attachment 5: The Drug Substance and Drug Product Specifications originally proposed in the NDA are provided (NDA pg. 02-012 to 02-013, & 02-024). Additionally, Amendments 3, 4 and 5, dated May 12th 2000, May 17th 2000 and May 18th 2000 are provided. These amendments contain the modifications proposed to the drug substance and drug product specifications as per the Agency requests. Please also refer to Amendment 6, dated May 19th 2000, provided in Attachment 2. A summary of these proposed modifications to the drug product specifications is also included for convenience.
6. Attachment 6: Table of Analytical Results for Drug Product (NDA pg. 02-025) and Certificates of Analyses of the Drug Substance and Drug Product Lots (NDA pg. 07-149 to 07-161) are provided.
7. Attachment 7: Drug Product Microbiological Test Methods (NDA pg.05-217 to 05-256).

We have confirmed with Santen Oy (Finland) that the samples are available for shipment or pick-up. The Agency may either call me, or Santen Oy, Finland (contact persons - Timo Reunamäki, Minna Lintusalo or Eija Selkänaho) directly at 011 358 3284 8420, to obtain the samples.

As per your request three (3) copies of this amendment are being sent to your attention. If there are any questions regarding this, please contact me at 707-256-2451. We look forward to hearing from you.

Sincerely,



Margaret Reents Timms
Vice-President, Regulatory Affairs and Project Management

Copies: Original & 2 copies
Mr. Mike Puglisi, Project Manager (cover letter only)



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755



22 June 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

NDA ORIG AMENDMENT

SU

RE: 120-day Safety Update Report
NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
A.011

Dear Dr. Chambers:

According to 21 CFR 314.50 (d) (5) (vi) (b), this submission contains the an update of safety information since the initial filing of NDA 21-199 on February 29, 2000 .

There has been no new safety information learned about the drug product which would reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

No new clinical studies have been conducted since the submission of the NDA.

If there are any questions regarding this amendment, please contact me at (707) 254-2453.

Sincerely,

Margaret Reents Timms
Vice-President, Regulatory Affairs and Project Management

Cc: Original, 2 copy
Mike Puglisi, Project Manager

DUPLICATE



SANTEN INCORPORATED

555 Gateway Drive
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NDA ORIG AMENDMENT



August 4, 2000

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

BL

RE: NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)
Proposed Package Insert

Dear Dr. Chambers:

Thank you for clarifying the Agency's comments on the QUIXIN package insert (7/31 teleconference). This amendment contains a revised package insert, which incorporates the majority of your recommendations.

Regarding the *in vitro* section, ocular pathogens listed in the package insert for the systemic levofloxacin products have been added. The majority of these organisms are listed in the package inserts for Ciloxan® or Ocuflax® package inserts and/or they were observed in patient(s) in our clinical trials. We have included a compilation of this information in the accompanying table for ease of review. Please note that it does appear that several of the organisms listed in the Ciloxan package insert were obtained only from the systemic clinical trials.

We have discussed the dosing regimen with numerous corneal experts and microbiologists and still feel strongly that the instructions for the 5-day regimen is appropriate. Information supporting this position is appended. We would appreciate the opportunity to discuss this topic with you further.

We are looking forward to hearing from you. I can be reached at 707-256-2453 and Maggie Timms can be reached at 707-256-2451. Thank you in advance for your assistance.

Sincerely,

Michelle Carpenter
Director, Regulatory Affairs

DUPLICATE

cc: Archival Copy
Review Copy



SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755



15 August 2000

Wiley Chambers, M.D
Deputy Division Director
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

AMENDMENT

BL

RE: **NDA #21-199, Levofloxacin Ophthalmic Solution, 0.5% (QUIXIN™)**
Final Labeling Text
A.012

Dear Dr. Chambers:

This amendment contains the final package insert for NDA 21-199, Levofloxacin Ophthalmic Solution, 0.5%. This is the same version sent to you by facsimile earlier today, which the Agency indicated was acceptable.

Thank you for your continued assistance. If there are any questions regarding this amendment, please please contact me at 707-256-2453.

Sincerely,

Michelle Carpenter
Director, Regulatory Affairs

Enclosures: Original, 2 copy
Mike Puglisi, Project Manager

DUPLICATE