CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-199

ADMINISTRATIVE DOCUMENTS

Santen

SANTEN INCORPORATED

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

Levofloxacin Ophthalmic Solution, 0.5%

Patent Information and Certification

Item 13 Patent Information

1) Patent Number and Date of Expiration

   a) Patent #: 4,382,892
      Expiry Date: September 2, 2003

   b) Patent #: 5,503,407
      Expiry Date: October 1, 2008

   c) Patent #: 4,551,456
      Expiry Date: November 14, 2003

2) Type of Patent (drug, drug product or method of use):

   a) 4,382,892: drug

   b) 5,503,407: drug and method of use

   c) 4,551,456: method of use

3) Name of Patent Holder:

   Daiichi Pharmaceutical Co, Ltd.
   Akita, Japan

4) Name of US representative authorized to receive notice of patent certification:

   Jennifer Benenson, Esq.
   General Counsel
   Daiichi Pharmaceutical Corporation

Declaration:

The undersigned declares that Patent Nos. 4,382,892, 5,503,407, and 4,551,456 cover the formulation, composition and/or method of use for 0.5% levofloxacin ophthalmic solution. This product is the subject of this application for which approval is being sought.

Item 14 Patent Information

Not applicable.

Margaret Reents Timms
Vice President, Regulatory
Affairs & Project Management
Santen Incorporated

2-14-2000
Date

EXCLUSIVITY SUMMARY for NDA # 21-199 SUPPL #_____

Trade Name QUIXIN Generic Name Levofloxacin Ophthalmic Solution, 0.5%

Applicant Name Santen, Inc. HFD-550

Approval Date, if known 8/18/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-634 Levaquin Tablets

NDA# 20-635 Levaquin Injection

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /✓/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   _____

   _____

   YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol 03-003 _____

Protocol 03-004 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # [ ] YES /✓/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # [ ] YES /✓/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/ 8/16/00

Signature Date

Title: Deputy Division Director

/S/ 8/16/00

Signature of Division Director Date

Deputy

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Santen

SANTEN INCORPORATED

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

Levofloxacin Ophthalmic Solution, 0.5%

(NDA 21-199)

Exclusivity Statement

Exclusivity: Three years of exclusivity is claimed under 314.108 (b) (4).

Pursuant to 21 CFR 314.50 (j) (4) and 314.108 (b) (4), Santen Incorporated certifies that this application contains new clinical investigations that are essential to approval of the application and were conducted by the Sponsor.

Margaret Reents Timms
Vice President, Regulatory
Affairs & Project Management
Santen Incorporated

2 - 14 - 2000
Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21199	**Trade Name:**	QUDXIN(LEVOFLOXACIN OPHTHALMIC SOLUTION
Supplement Number:		**Generic Name:**	LEVOFLOXACIN OPHTHALMIC SOLUTION 0.5%
Supplement Type:		**Dosage Form:**	Solution/Drops; Ophthalmic
Regulatory Action:	AP	**Proposed Indication:**	Treatment of bacterial conjunctivitis

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
_X_ Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Safety and effectiveness in infants below the age of one year have not been established.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MICHAEL PUGLISI

/S/ July 26, 2000

Signature Date

Santen

SANTEN INCORPORATED

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

Levofloxacin Ophthalmic Solution, 0.5%

(NDA 21-199)

Debarment Certification

Santen Incorporated certifies that it did not and will not use in any capacity the services of any individual debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug and Cosmetic Act, as amended, 21 U.S. C. §§ 335 (a) and (b), in connection with this application.

Margaret Reents Timms
Vice President, Regulatory
Affairs & Project Management
Santen Incorporated

2-14-2000
Date

Deputy Division Director Memorandum for NDA 21-199

NDA #21-199 Date: 8/18/2000

Name:	QUIXIN™ (levofloxacin hemihydrate ophthalmic solution) 0.5%
Sponsor:	Santen Inc. 555 Gateway Drive, Napa, CA 94558 (707) 254-1750
Pharmacologic Category:	Anti-infective (fluoroquinolone)
Proposed Indication(s):	Bacterial conjunctivitis
Dosage Form:	Ophthalmic solution
Route(s) of Administration:	Topical ophthalmic administration
NDA Drug Classification:	3 P

This memorandum is to resolve potential conflicts between primary reviews.

Statistical Review

The Statistical Review concluded that the sponsor did not demonstrate superiority of levofloxacin over vehicle because clinical cure was not the protocol's specified endpoint and therefore a statistical adjustment for using an additional endpoint is necessary. This conclusion is contrary to CDER's long standing precedent that the only acceptable endpoint for bacterial conjunctivitis is clinical cure. The agency has used this endpoint for each of the products reviewed (approved or not approved) for bacterial conjunctivitis over the past 13 years. As stated in the Medical Officer's Review, the studies demonstrate superiority of levofloxacin over vehicle with respect to clinical cure and equivalence to ofloxacin ophthalmic solution with respect to clinical cure.

Manufacturing site inspections

The Chemistry/Manufacturing Review has recommended approval pending satisfactory Establishment Inspection Reports of the manufacturing/testing sites. Acceptable reports have been received for all but one site. The one site for which an acceptable report has not been received is scheduled to have an inspection starting in approximately 1 month. This site [redacted] is responsible only for sterility testing and received an acceptable inspection at the time of its last inspection (February 22, 1995). Consistent with FDAMA (i.e., No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug) this application will be recommended for approval because the Division has no evidence that a delay is necessary to assure the marketing of a safe and effective drug.

Conclusions/ Recommendations

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

Wiley A. Chambers, M.D.
Deputy Division Director
Division of Anti-inflammatory, Analgesic and
Ophthalmologic Drug Products

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Timm Carpenter	Executive Vice President, Chief Financial Officer
FIRM/ORGANIZATION: Santen, Inc.	
SIGNATURE: [signature]	DATE: 2-7-00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

LIST OF INVESTIGATORS, NDA AND IND NUMBERS

Study Number	Clinical Investigator	Study Site Address	Location of Final Study Report. Volume/Page
Phase I Clinical Studies			
03-001	Rubin, JM **Sub-Investigators** Shulman, DG	999 East Basse Road, Ste. 128B San Antonio, TX 78209	
03-005	Laurent, AL **Sub-Investigators** Hunt, TL Wong, S	PPD Pharmaco, Inc., Clinics 706A Ben White Boulevard West Austin, TX 78704	
03-006	Rubin, JM **Sub-Investigator** none	999 East Basse Road, Ste. 128B San Antonio, TX 78209	
Phase II Clinical Studies			
03-002	Assil, K **Sub-Investigator** Bahadur, GG	The Sinskey Eye Institute 2232 Santa Monica Blvd. Santa Monica, CA 90411	
	Shulman, DG **Sub-Investigator** Rubin, JM	999 East Basse Road, Ste. 128B San Antonio, TX 78209 8478 Fredricksburg Rd. San Antonio, TX 78229	
	Wapner, FJ **Sub-Investigator** Stanford, GB	Advanced Eye Care 1250 E. 3900 South, Suite 310 Salt Lake City, UT 84124	

Phase III Clinical Studies		
03-003	Abelson, M	863 Turnpike Street, Suite 224 North Andover, MA 01845
	Sub-Investigators	
	Chin, TLN	555 Turnpike St.
	Crampton, HJ	North Andover, MA 01845
	Greiner, JV	
	Michaelson, C	138 Haverhill St.
	Miller, D	Andover, MA 01810
	Rapoza, PA	
	Townend, DJ	
	Bahadur, G	The Sinskey Eye Institute 2232 Santa Monica Blvd.
	Sub-Investigator	Santa Monica, CA 90404
	Assil, KK	
	Braunstein, R	Harkness Eye Institute 635 W. 165th St., Box 39
	Sub-Investigator	*New York, NY 10032*
	Odrich, MG	
		16 East 60th St., Suite 420 New York, NY 10022
	Caine, R	110 Cambridge St. Fredericksburg, VA 22405
	Sub-Investigators	
	Friedman, R	
	Grossett, S	
	Kossol, W	
	Cavanaugh, T	The Hunkeler Eye Center 43321 Washington, Suite 6000
	Sub-Investigators	Kansas City, MO 64111
	Durrie, DS	
	Karpecki, P	Hunkeler Eye Study Center
	King, BJ	4320 Wornall Suite 520
	Linn, SH	Kansas City, MO 64111
	Moyes, AL	
	Thompson, SBL	
	Uhl, J	
	Wachler, BB	

Dell, SJ	Texan Eye Care 1700 S. Mopac Austin, TX 78746
Sub-Investigators	
Montgomery, JE McMenemy, MG Sargent, JB	Texan Eye Care 1020 W. 34th Street Austin, TX 78705
Donshik, P	29 N. Main Street West Hartford, CT 06197-1933
Sub-Investigators	
Ehlers, W Shelton, P Suchecki, J	54 W. Avon Road West Hartford, CT 06001
Friedlaender, M	Scripps Clinic and Research Foundation MS 214 10666 N. Torrey Pines Road La Jolla, CA 92037
Sub-Investigator none	
Lichtenstein, SJ	Metro United Way Building Suite 325 334 East Broadway Louisville, KY 40202
Sub-Investigator none	
Levy, NS	Florida Ophthalmic Institute 7100 NW 11th Place Gainesville, FL 32605-3192
Sub-Investigator Levy, D	
McCulley, J	UT Southwestern Medical Center – Dallas Department of Ophthalmology 5323 Harry Hines Blvd. Dallas, TX 75235-9057
Sub-Investigators	
Bowman, RW Cavanaugh, HD Hargraave, SL Want, SX Weakley, DR Jr.	Parkland Memorial Hospital 5201 Harry Hines Blvd. Dallas, TX 75235 Childrens Med. Ct. of Dallas 1935 Motor St. Dallas, TX 75235

	Schwab, IR Mannis, MJ **Sub-Investigator** none	Department of Ophthalmology Univ. of California Davis 1603 Alhambra Blvd. Sacramento, CA 95816 Ellison Ambulatory Care Center 4860 Y Street, Suite 2400 Sacramento, CA 95817
	Sugar, A **Sub-Investigators** Meyer, RF Soong, HK	Kellogg Eye Center Univ. of Michigan 1000 Wall Street Ann Arbor, MI 48105-1994
	Valluri, S **Sub-Investigator** none	Indiana University 702 Rotary Circle Indianapolis, IN 46202 550 N. University Blvd. Suite 3005-3073 Indianapolis, IN 46202
	Wapner, FJ **Sub-Investigator** Stanford, GB	Advanced Eye Care 1250 E 3900 South, #310 Salt Lake City, UT 84124
	Wolfe, T **Sub-Investigators** Chodosh, J Razook, J	Dean McGee Eye Institute 608 Stanton Young Blvd. Oklahoma City, OK 73104
03-004	Casey, R **Sub-Investigator** Flowers, CW	King-Drew Medical Center 1202 S. Wilmington Ave., Room 5009 Los Angeles, CA 90059 4560 Admiralty Way, Suite 354 Marina Del Rey, CA 90292 University of California, Los Angeles Jules Stein Eye Institute 100 Stein Plaza 3-217 Los Angeles, CA 90024

Cerise, D **Sub-Investigators** Stumpf, GC McGinn, T	4324 Veterens Blvd. Metarie, LA 70006
Crabb, I. **Sub-Investigator** McQuirter, H	Eye Tech 5496 Knight Arnold Rd. Memphis, TN 38115
Forstot, SL **Sub-Investigator** Damino, RE	8381 Southpark Lane Littleton, CO 80120
Foulks, G **Sub-Investigators** Goldstein, M Hu, D	University of Pittsburgh Department of Ophthalmology 203 Lothrop Street, Room 817 Pittsburgh, PA 15213
Hwang, D **Sub-Investigators** Holsclaw, D Lee, SM McLeod, SD	University of California, San Francisco 10 Kirkham Street K-301 Boox 0730 San Francisco, CA 94143-0730
Kretchman, G **Sub-Investigator** Folk, AG	1010 E. McDowell #406 Phoenix, AZ 85006 10585 N. Tatum Blvd., Ste. #D131 Paradise Valley, AZ 85253 2337 W. Northern Phoenix, AZ 85021
Montgomery, JE **Sub-Investigator** Sargent, JB	Texan Eye Care 1700 S. Mopac Austin, TX 78746 Texan Eye Care 1020 W. 34th Street Austin, TX 78705

Raizman, M	New England Medical Center 750 Washington Street
Sub-Investigators	Boston, MA 02111
Rothman, J	
Lee, Y	
Wu, H	
McColgin, A	
McDonald, T	
Laird, K	
Conti, E	

Rotberg, MH	Charlotte Eye, Ear, Nose and Throat Associates, PA
Sub-Investigators	1600 E. Third Street
Alter, GJ	Charlotte, NC 28204
Antoszyk, AN	
Antoszyk, JH	Park Crossing Medical Center
Bourgeois, JE	10352 Park Road
Browning, DJ	Charlotte, NC 28210
Culton, JC	
Flores, RA	101 W.T. Harris Blvd., Suite 5103
Jaben, SL	Charlotte, NC 28260
Kansupada, KB	
Kreshon, M	1450 Matthews Township
Saunders, TG	Parkway
Stewart, DH	Suite 110
Sutherland, FS	Matthews, NC 28105
Weaver, JE	
Young, JA	701 East Roosevelt Blvd. Monroe, NC 28112
	209 Park Street, Suite 600 Belmont, NC 28012

Rubin, JM	999 E. Basse Road. #128B San Antonio, TX 78209
Sub-Investigator	
none	

Schanzlin, DJ	Shiley Eye Center University of California, San
Sub-Investigators	Diego
Granet, DB	9500 Gilman Drive, Dept. 0946
Twa, MD	La Jolla, CA 92093-0946

Shulman, DG **Sub-Investigators** Linenberger, SK Rubin, JM	999 E. Basse Road, #116 San Antonio, TX 78209
Terry, M **Sub-Investigators** Wilkins, JH	Devers Eye Institute 1040 NW 22nd Avenue Suite 200 Portland, OR 97210-3065
Zloty, P **Sub-Investigators** Bennett, W Dannemann, A	Eye Institute of the South 2800 Ross Clark Circle, SW Dothan, AL 36301

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 6/1/00

NDA#: 21-199

NAME OF DRUG: Quixin (Levofloxacin Ophthalmic Solution) 0.5%

NDA HOLDER: Santen, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory Analgesic, and Ophthalmic Drug Products (HFD-550) on 3/18/00, to review the proposed proprietary drug name, Quixin, in regard to potential name confusion with existing proprietary/generic names.

PRODUCT INFORMATION

Quixin (levofloxacin ophthalmic solution 0.5%) is a sterile topical ophthalmic solution. It is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens. Each mL of Quixin 0.5% contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin. Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. Levofloxacin is thought to exert a bactericidal effect on susceptible bacterial cells by inhibiting DNA gyrase, an essential bacterial enzyme that is a critical catalyst in the duplication, transcription, and repair of bacterial DNA.

Quixin solution is indicated for the treatment of bacterial conjunctivitis in patients > 1 year of age due to susceptible strains of organisms. It is recommended to instill one to two drops in the affected eye(s) every 2 hours while awake up to 8 times per day during day 1 and 2. From day 3 through 5, use one to two drops in the affected eye(s) every 4 hours while awake up to 4 times a day.

Quixin will be supplied in a white, polyethylene bottle with a controlled dropper tip in 2.5 mL and 5 mL.

Levofloxacin is also available as 250 mg, 500 mg tablets, and 250 mg and 500 mg injection under the trade name, Levaquin.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Quixin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The expert panel expressed some concerns with existing approved product, Floxin which sounds like Quixin. However, Quixin will be available as 0.5% ophthalmic solution and Floxin is an otic solution. There is no overlapping strength, and dosing intervals between these two products.

Product Name	Dosage form (s) / Generic name	Usual Dose	Observation
Quixin	Ophthalmic soln 0.5% 2.5 & 5 ml / levofloxacin	1-2 drops q2h up to 8 times a day in day 1 and 2; 1-2 drops q4h up to 4 times a day in day 3 through 5	
Floxin	Otic solution, 0.3% 5 ml, ofloxacin	5-10 drops bid for 10-14 days	*SA

*SA = Sound-alike

The panel concluded that the above listed drug and Quixin pose no significant safety risk due to name confusion, and therefore, the proprietary name, Quixin, is not objectionable.

2. DDMAC – no objection

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Quixin with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Quixin (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

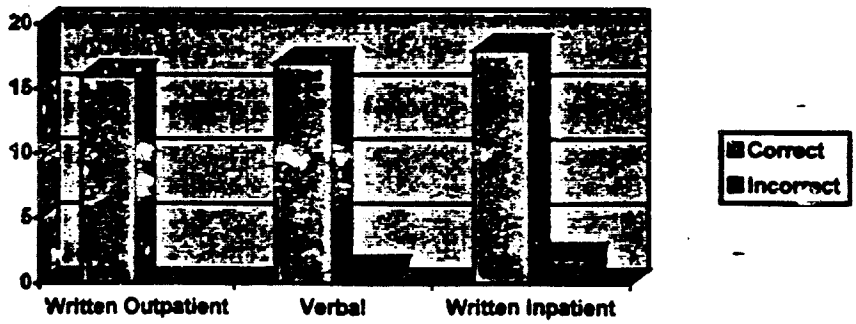
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Quixin #1 Sig: One gtt od q2h x 2 days	Quixin #1 Sig: One gtt od q2h x 2 days
Inpatient RX: Quixin one gtt OD q2h x 2 days	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	32	16(50%)	16	0
Verbal	31	18(58%)	17	1
Written Inpatient	31	20(66%)	18	2
Total	94	54(57%)	51(94%)	3(6%)



Ninety-four percent of the participants responded with the correct name, Quixin. The incorrect written and verbal responses are as follows in Table II.

Table II

	Incorrectly interpreted
Written Inpatient	Quixiri (2)
Verbal	Quickson

C. SAFETY EVALUATOR RISK ASSESSMENT

Floxin otic solution was identified to have potential for confusion with Quixin due to its sound-alike similarities. Both drugs are available in topical solutions even though one is for ophthalmic use and the other is for otic use. Both are available in a 5 mL bottle. However, despite these similarities, Quixin and Floxin differ in terms of dose, strength and dosing interval.

The results of the verbal prescription study indicates that one (out of eighteen) participants interpreted Quixin incorrectly. In the written outpatient and inpatient studies, sixteen (out of sixteen) interpreted Quixin correctly and only three (out of twenty written inpatient) interpreted Quixin incorrectly. These incorrect responses were misspelled/phonetic variation of the drug name, Quixin. Finally, in all three studies, we did not uncover any overlapping existing drug names. Because of the size of the study, this does not provide persuasive evidence that an error might not occur when exposed to the general population.

LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Quixin, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

[redacted]

B. CARTON LABELING

[redacted]

B. INSERT LABELING

[redacted]

IV. RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name, Quixin.

2. OPDRA recommends the above labeling revisions which might lead to safe use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241

/S/ 6/2/00

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 6/2/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 3/18/00	DUE DATE: 6/1/00	OPDRA CONSULT #: 00-0096

TO:
Karen Midthun, M.D.
Director, Division of Anti-Inflammatory Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH:
Mike Puglisi
Project Manager
HFD-550

PRODUCT NAME:	MANUFACTURER: Santen Inc.
Quixin (levofloxacin Ophthalmic Solution) 0.5% **NDA #: 21-199**	

SAFETY EVALUATOR: P. Tam, RPh.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Quixin. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

✓ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 6/5/00

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration