

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-537

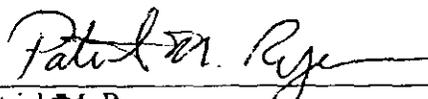
**ADMINISTRATIVE DOCUMENTS AND
CORRESPONDENCE**

3.A.2. Patent Certification

Following are listed all patents known to the applicant that claim the drug or method of using the drug that is the subject of this new drug application and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Patent Number:	4,844,902
Owner:	Bayer Aktiengesellschaft
Claim Type:	Drug Product
Expiration Date:	02/11/08
Patent Number:	6,284,804
Owner:	Alcon, Inc.
Claim Type:	Drug Product
Expiration Date:	08/10/20
Patent Number:	6,359,016
Owner:	Alcon, Inc.
Claim Type:	Drug Product
Expiration Date:	08/10/20

The undersigned declares that U.S. Patent Nos. 4,844,902, 6,284,804 and 6,359,016 cover the composition, formulation, and/or method of use of CIPRODEX[®] OTIC (ciprofloxacin 0.3% HCl and dexamethasone 0.1% otic suspension). This product is the subject of this application for which approval is being sought.


 Patrick M. Ryan
 Assistant General Counsel
 Tel. 817-551-3066

8/13/02
 Date

Patent Information Pursuant to 21 C.F.R. 314.53 for NDA #21-537

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: CIPRODEX®
Active Ingredient(s): ciprofloxacin; dexamethasone
Strength(s): 0.3%; 0.1%
Dosage Form: Suspension, Otic
Approval Date: July 18, 2003

U.S. Patent Number:	4,844,902
Expiration Date:	February 11, 2008
Type of Patent:	1. Drug Substance (active ingredient): 2. Drug Product (composition/formulation): Yes 3. Method of Use:
Name of Patent Owner:	Bayer Aktiengesellschaft Leverkusen, Germany
U.S. Agent:	Sprung Horn Kramer & Woods

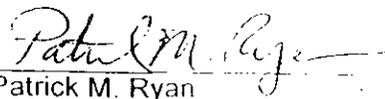
U.S. Patent Number:	6,284,804
Expiration Date:	August 10, 2020
Type of Patent:	1. Drug Substance (active ingredient): 2. Drug Product (composition/formulation): Yes 3. Method of Use:
Name of Patent Owner:	Alcon, Inc. Hunenberg, Switzerland
U.S. Agent:	Alcon Research, Ltd., Patent Department

U.S. Patent Number:	6,359,016
Expiration Date:	February 11, 2008
Type of Patent:	1. Drug Substance (active ingredient): 2. Drug Product (composition/formulation): Yes 3. Method of Use:
Name of Patent Owner:	Alcon, Inc. Hunenberg, Switzerland
U.S. Agent:	Alcon Research, Ltd., Patent Department

The undersigned declares that the above stated United States Patent Numbers 4,844,902; 6,284,804; and 6,359,016 cover the drug substance, composition and/or method of use of CIPRODEX® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

On behalf of Alcon, Inc.

Signed:


Patrick M. Ryan

Date:

8/14/03

Telephone No.

817-551-3066

3. Administrative Documents

3.A. Administrative Documents

3.A.1. PATENT INFORMATION

A. Patents

Pursuant to 21 CFR §314.53, the applicant hereby submits information on each patent that claims the drug or a method of using the drug that is the subject of this new drug application and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Patent Number:	4,844,902
Owner:	Bayer Aktiengesellschaft
Claim Type:	Drug Product
Expiration Date:	02/11/08
Patent Number:	6,284,804
Owner:	Alcon, Inc.
Claim Type:	Drug Product
Expiration Date:	08/10/20
Patent Number:	6,359,016
Owner:	Alcon, Inc.
Claim Type:	Drug Product
Expiration Date:	08/10/20

United States Patent [19]
Grohe

[11] Patent Number: **4,844,902**
[45] Date of Patent: **Jul. 4, 1989**

[54] **TOPICALLY APPLICABLE
FORMULATIONS OF GYRASE INHIBITORS
IN COMBINATION WITH
CORTICOSTEROIDS**

[75] Inventor: **Klaus Grohe, Odenthal, Fed. Rep. of
Germany**

[73] Assignee: **Bayer Aktiengesellschaft,
Leverkusen, Fed. Rep. of Germany**

[21] Appl. No.: **154,835**

[22] Filed: **Feb. 11, 1988**

[30] **Foreign Application Priority Data**

Feb. 17, 1987 [DE] Fed. Rep. of Germany 3704907

[51] Int. Cl.⁴ **A61F 13/00**

[52] U.S. Cl. **424/449; 424/447**

[58] Field of Search **424/449**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,659,603 4/1987 Groke et al. 514/254
4,681,876 7/1987 Marpla et al. 514/182

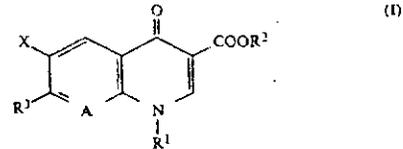
OTHER PUBLICATIONS

BE-A- 829 197 (L. Grosjean);
GB-A-2 116 425 (Rhom Pharma).
Embase 86048074, 0150500902110.

Primary Examiner—Ellis P. Robinson
Assistant Examiner—Leon R. Horne
Attorney, Agent, or Firm—Sprung Horn Kramer &
Woods

[57] **ABSTRACT**

Topically applicable formulations comprising known ciprofloxacin-type antibacterials of the formula



in which

A is N or C-R⁹,

and corticosteroids are especially effective in therapy, particularly in the oral cavity. The formulations can be used in the form of plasters, gels, suspensions, emulsions and solutions.

11 Claims, No Drawings

**APPEARS THIS WAY
ON ORIGINAL**



US006284804B1

(12) **United States Patent**
Singh et al.

(10) Patent No.: **US 6,284,804 B1**
(45) Date of Patent: **Sep. 4, 2001**

(54) **TOPICAL SUSPENSION FORMULATIONS CONTAINING CIPROFLOXACIN AND DEXAMETHASONE**

WO 90/01933 3/1990 (WO) .
00/18386 4/2000 (WO) .
00/18387 4/2000 (WO) .
00/18388 4/2000 (WO) .
00/18404 4/2000 (WO) .

(75) Inventors: **Onkar N. Singh, Arlington; Haresh G. Bhagat, Fort Worth, both of TX (US)**

OTHER PUBLICATIONS

(73) Assignee: **Alcon Universal Ltd., Huneberg (CH)**

Product insert for Vexol® 1% (Rimexolone Ophthalmic Suspension).

(*) Notice: **Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**

Engel et al., "Effectiveness of Specific Antibiotic/Steroid Combinations for Therapy of Experimental *Pseudomonas aeruginosa* Keratitis," *Current Eye Research*, pp. 229-234 (1994).

(21) Appl. No.: **09/636,563**

Hobden et al., "Ciprofloxacin and Prednisolone Therapy for Experimental *Pseudomonas* Keratitis," *Current Eye Research*, vol. 11(3), pp. 259-266 (1992).

(22) Filed: **Aug. 10, 2000**

Hobden et al., "Prednisolone Acetate or Prednisolone Phosphate Concurrently Administered With Ciprofloxacin for the Therapy of Experimental *Pseudomonas Aeruginosa* Keratitis," *Current Eye Research*, vol. 12(5), pp. 469-473 (1993).

Related U.S. Application Data

(60) Provisional application No. 60/155,942, filed on Sep. 24, 1999.

"Biamotil-D" Product Insert.

(51) Int. Cl.⁷ **A61K 47/32; A61K 31/74; A61K 31/56**

"Steroid and Antibiotic Solutions and Suspensions," *Ophthalmic Drug Facts* 1999, pp. 121-122 (1999).

(52) U.S. Cl. **514/772.4; 514/912; 514/169; 514/171; 424/78.04**

Doshi et al., "Preparation and Evaluation of New Eye-Drops Containing a Combination of Ciprofloxacin and Dexamethasone," *Indian Drugs*, vol. 37(4), pp. 190-195 (2000).

(58) Field of Search **424/78, 427, 428, 424/85; 514/772.4, 912, 169, 171**

Sucker et al., "Pharmazeutische Technologie," *Thieme Verlag*, pp. 643-661 (1992).

(56) **References Cited**

Ciloxan® Product Information, *Physicians' Desk Reference for Ophthalmology*, pp. 209-211 (1998).

U.S. PATENT DOCUMENTS

* cited by examiner

3,134,718	5/1964	Nobile	167/65
4,670,444	6/1987	Grobe et al.	514/300
4,686,214	8/1987	Boltralik	514/179
4,844,902	7/1989	Grobe	424/449
5,223,493	6/1993	Boltralik	514/180
5,420,120	5/1995	Boltralik	514/172
5,540,930	7/1996	Guy et al.	424/427
5,679,336	10/1997	Ali et al.	424/78.04
5,747,061	5/1998	Amselem et al.	424/427
5,843,930	12/1998	Purwar et al.	514/171
5,863,841	1/1999	Liedtke	514/555

FOREIGN PATENT DOCUMENTS

0 661 055 A1	7/1995	(EP) .
0 868 919 A2	10/1998	(EP) .
2065846	8/1995	(ES) .
WO-90/01933 *	3/1990	(WO) .

Primary Examiner—Thurman K. Page
Assistant Examiner—Blessing Fubara
(74) Attorney, Agent, or Firm—Patrick M. Ryan

(57) **ABSTRACT**

Suspension formulations containing dexamethasone and ciprofloxacin are disclosed. The formulations contain a nonionic polymer, a nonionic surfactant and an ionic tonicity agent, but are physically stable and easily re-suspended. The formulations are intended for topical application to the eye, ear or nose.

1 Claim, No Drawings

**APPEARS THIS WAY
ON ORIGINAL**



US006359016B2

(12) **United States Patent**
Singh et al.

(10) Patent No.: **US 6,359,016 B2**
(45) Date of Patent: ***Mar. 19, 2002**

- (54) **TOPICAL SUSPENSION FORMULATIONS CONTAINING CIPROFLOXACIN AND DEXAMETHASONE**
- (75) Inventors: **Onkar N. Singh, Arlington; Haresh G. Bhagat, Fort Worth, both of TX (US)**
- (73) Assignee: **Alcon Universal Ltd., Hunenberg (CH)**
- (*) Notice: **Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**

This patent is subject to a terminal disclaimer.

EP	0 868 919 A2	10/1998
ES	2065846	8/1995
WO	90/01933	3/1990
WO	90/01933	3/1999
WO	00/18386	4/2000
WO	00/18387	4/2000
WO	00/18388	4/2000
WO	00/18404	4/2000

OTHER PUBLICATIONS

Database Registry on STN, American Chemical Society, (Columbus, OH, USA).*

"Biamotil-D" Product Insert.

Ciloxan® Product Information, *Physicians' Desk Reference for Ophthalmology*, pp. 209-211 (1998).

Doshi et al., "Preparation and Evaluation of New Eye-Drops Containing a Combination of Ciprofloxacin and Dexamethasone," *Indian Drugs*, vol. 37(4), pp. 190-195 (2000).

Engel et al., "Effectiveness of Specific Antibiotic/Steroid Combinations for Therapy of Experimental *Pseudomonas aeruginosa* Keratitis," *Current Eye Research*, pp. 229-234 (1994).

Hobden et al., "Ciprofloxacin and Prednisolone Therapy for Experimental *Pseudomonas* Keratitis," *Current Eye Research*, vol. 11(3), pp. 259-266 (1992).

Hobden et al., "Prednisolone Acetate or Prednisolone Phosphate Concurrently Administered With Ciprofloxacin for the Therapy of Experimental *Pseudomonas Aeruginosa* Keratitis," *Current Eye Research*, vol. 12(5), pp. 469-473 (1993).

"Steroid and Antibiotic Solutions and Suspensions," *Ophthalmic Drug Facts 1999*, pp. 121-122 (1999).

Sucker et al., "Pharmazeutische Technologie," *Thieme Verlag*, p. 643-661 (1992).

Vexol® 1% (Rimexolone Ophthalmic Suspension) Product Insert.

- (21) Appl. No.: **09/865,783**
- (22) Filed: **May 25, 2001**

Related U.S. Application Data

- (63) Continuation of application No. 09/636,563, filed on Aug. 10, 2000, now Pat. No. 6,284,804.
- (60) Provisional application No. 60/155,942, filed on Sep. 24, 1999.
- (51) Int. Cl.⁷ **A61K 47/32; A61K 31/56; A61K 31/74**
- (52) U.S. Cl. **514/772.4; 514/912; 514/169; 514/171; 424/78.04**
- (58) Field of Search **514/772.4, 777, 514/912, 913, 914, 915, 950, 954, 955, 964; 424/427, 428, 485, 488, 78.04**

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,124,718 A	5/1964	Nobile	167/65
4,670,444 A	6/1987	Grohe et al.	514/300
4,686,214 A	8/1987	Boltralik	514/179
4,844,902 A	7/1989	Grohe	424/449
5,223,493 A	6/1993	Boltralik	514/180
5,420,120 A	5/1995	Boltralik	514/172
5,422,116 A	6/1995	Yea et al.	424/427
5,540,930 A	7/1996	Guy et al.	424/427
5,679,336 A	10/1997	Ali et al.	424/78.04
5,747,061 A	5/1998	Amselem et al.	424/427
5,843,930 A	12/1998	Purwar et al.	514/171
5,863,941 A	1/1999	Liedtke	514/555
6,284,804 B1	9/2001	Singh et al.	514/772.4

FOREIGN PATENT DOCUMENTS

EP 0 661 055 A1 7/1995

* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Blessing Fubara
(74) Attorney, Agent, or Firm—Patrick M. Ryan

(57) **ABSTRACT**

Suspension formulations containing dexamethasone and ciprofloxacin are disclosed. The formulations contain a nonionic polymer, a nonionic surfactant and an ionic tonicity agent, but are physically stable and easily re-suspended. The formulations are intended for topical application to the eye, ear or nose.

5 Claims, No Drawings

EXCLUSIVITY SUMMARY for NDA # 21-537 SUPPL #
Trade Name Ciprodex Sterile Otic Suspension
Generic Name ciprofloxacin 0.3% and dexamethasone 0.1%

Applicant Name Alcon Research, Ltd. HFD-520
Approval Date July 18, 2003

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 questions 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?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9.

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 9 (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 #

NDA #

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 / _____ /

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

- NDA # 20-805, Cipro HC
- NDA # 11-984, Decadron Ophthalmic/Otic Solution
- NDA # 84-855, Dexamethasone Sodium Phosphate Otic Solution
- NDA # 88-771, Dexamethasone Sodium Phosphate Ophthalmic Otic Solution
- NDA # 40-069, Dexamethasone Sodium Phosphate Ophthalmic Otic Solution

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 9.

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 (a) 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.

For the purposes of this section, studies comparing two products with the same ingredients are considered to be bioavailability studies.

- (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 9:

- (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 NC.

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:

- Investigation #1, Study # C-98-18

Investigation #2, Study # C-98-19

Investigation #3, Study # C-99-59

Investigation #4, Study # C-00-52

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 / /

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (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 / <input checked="" type="checkbox"/> /
Investigation #2	YES /__ /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES /__ /	NO / <input checked="" type="checkbox"/> /
Investigation #4	YES /__ /	NO / <input checked="" type="checkbox"/> /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (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"):

Investigation #1, Study # C-98-18
Investigation #2, Study # C-98-19
Investigation #3, Study # C-99-59
Investigation #4, Study # C-99-52

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(s) #1,2,3,4 !

IND # 54,670 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?

Not Applicable

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: _____

Daniel Nguyen 
Signature of Preparer
Title: Regulatory Health Project Manager

Date 9-8-03

Janice Soreth 
Signature of Office or Division Director

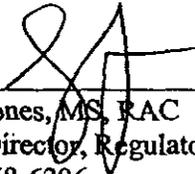
Date 9/8/03

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

3.A.3. DEBARMENT CERTIFICATION

Alcon, Inc. and its affiliated companies, Alcon Research Ltd., and Alcon Laboratories Inc., hereby certify that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.


Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs
Tel. 817-568-6296

8/23/02

Date

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: 21-537 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 09-25-02 Action Date: 07-18-03

HFD 520 Trade and generic names/dosage form: Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension

Applicant: Alcon Research, Ltd. Therapeutic Class: Anti-Infective Otic Combination

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Acute Otitis Media in pediatric patients (age 6 months and older) with tympanostomy tubes due to Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Pseudomonas aeruginosa.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns

- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

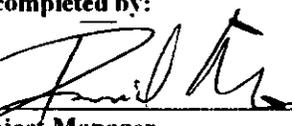
Age/weight range of completed studies:

Min _____	kg _____	mo. 6	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. 12	Tanner Stage _____

Comments: Studies included relevant pediatric age distribution for this indication. Product is labeled for ages 6 months and older.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Daniel Nguyen 

Regulatory Project Manager

cc: NDA
 HFD-950/ Terrie Crescenzi
 HFD-960/ Grace Carmouze
 (revised 9-24-02)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Acute Otitis Externa in pediatric (age 6 months and older), adult and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

— Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. <u>1</u>	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. <u>adult</u>	Tanner Stage _____

Comments: Studies included relevant pediatric age distribution for this indication. Product is labeled for ages 6 months and older.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Daniel Nguyen

Regulatory Project Manager



cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-537	Efficacy Supplement Type: NA	Supplement Number: NA
Drug: CIPRODEX [®] (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension		Applicant: Alcon Research Ltd.
RPM: Daniel Nguyen	HFD-520	Phone # 301-827-2216
Application Type: () 505(b)(1) (<input checked="" type="checkbox"/>) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NA
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		(<input checked="" type="checkbox"/>) Standard () Priority Type 3 NA
❖ User Fee Goal Dates		07-25-03
❖ Special programs (indicate all that apply)		(<input checked="" type="checkbox"/>) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver 		(<input checked="" type="checkbox"/>) Paid () Small business () Public health () Barrier-to-Innovation () Other
<ul style="list-style-type: none"> • User Fee exception 		() Orphan designation () No-fee 505(b)(2) () Other
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP • Exception for review (Center Director's memo) • OC clearance for approval 		() Yes (<input checked="" type="checkbox"/>) No () Yes (<input checked="" type="checkbox"/>) No
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		(<input checked="" type="checkbox"/>) Verified
❖ Patent		
<ul style="list-style-type: none"> • Information: Verify that patent information was submitted • Patent certification [505(b)(2) applications]: Verify type of certifications submitted 		(<input checked="" type="checkbox"/>) Verified 21 CFR 314.50(i)(1)(i)(A) () I () II () III () IV 21 CFR 314.50(i)(1) () (ii) () (iii) () Verified
<ul style="list-style-type: none"> • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). 		

Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 	✓
<ul style="list-style-type: none"> Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification! 	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	NA
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(✓) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	NONE
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(✓) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (✓) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(✓) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	✓ 07-17-03
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	✓ 07-15-03
<ul style="list-style-type: none"> Original applicant-proposed labeling 	✓ 09-23-02
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) 	✓ Trade Name Review 04-10-03 Labeling meetings: 07-07-03, 07-15-03, 07-17-03 (See Memos and Telecon Section)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	NA
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	✓ 07-17-03
<ul style="list-style-type: none"> Applicant proposed 	✓ 07-15-03
<ul style="list-style-type: none"> Reviews 	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	NA
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	Not held
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	✓ (03-29-02)
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	Not held
<ul style="list-style-type: none"> Other (Teleconferences) 	✓

Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	NA
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	✓ (08-07-03)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	✓ (07-21-03)
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NA
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	✓
❖ Statistical review(s) (indicate date for each review)	✓ (07-18-03)
❖ Biopharmaceutical review(s) (indicate date for each review)	✓ (07-18-03)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	✓ (04-25-03)
• Bioequivalence studies	NA
CMC Information	
CMC review(s) (indicate date for each review)	✓ (07-16-03)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Granted. (07-16-03)
• Review & FONSI (indicate date of review)	NA
• Review & Environmental Impact Statement (indicate date of each review)	NA
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	✓ (02-21-03)
❖ Facilities inspection (provide EER report)	Date completed: 04-07-03 (✓) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (✓) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	✓ (06-18-03, 07-01-03)
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

Airborne Express Airbill Number 4340372960

August 14, 2003

Dr. Janice M. Soreth, M.D.
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

N-000(XP)

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

NDA SUPPL AMENDMENT

RE: CIPRODEX® OTIC, NDA 21-537
Correspondence: Time Sensitive Patent Information

RECEIVED

AUG 15 2003

MEGA/CDER

Dear Dr. Soreth:

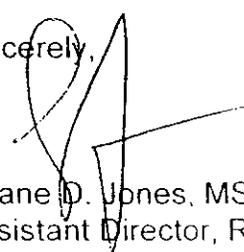
Pursuant to 21 CFR 314.53(c)(2)(i) attached please find time sensitive patent information for NDA 21-537, Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension.

The NDA was approved July 18, 2003. US patents 4,844,902, 6,284,804, and 6,359,016 claim the drug product, drug substance and method of use that was approved.

A copy of this information has also been submitted to the Information Services Team of the Division of Data Management and Services for publication in The Orange Book.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti Infective Drug Products
Information Services Team (Division of Data Management and Services)

MEMORANDUM OF TELECON

DATE: July 17, 2003

TIME: 11:15 AM LOCATION: S-346

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

Michael Wall, PhD	Sr. Director, Otic/Nasal Product Development
Shery Dupre, BS	Assistant Director, Otic Clinical Development
Peter Conroy, PhD, JD	Associate Director, Otic/Nasal Product Development
Celeste McLean, ASCP	Scientist II, Microbiology
David W. Stroman, PhD	Director, Anti-Infective Microbiology
Leslie Lemke, PhD	Sr. Scientist, Toxicology
Susan Potts, MS	Manager, Biostatistics-ENT and Anti-Infectives
Michael Pflieger, JD	Sr. Director, Regulatory Affairs
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs
Gale Cupp, MS	Principle Scientist, Microbiology
Chuck Inman, BS	Group Product Director, Otic
Heather Drennan, BS	Assistant Product Manager, Otic

Representing: Alcon Research Ltd. (Alcon)

AND

Name:

Janice Soreth, MD	Director, DAIDP
Jean Mulinde, MD	Medical Team Leader
Tom Smith, MD	Clinical Reviewer
Peter Kim, MD	Clinical Reviewer
Amy Ellis, PhD	Pharmacology/Toxicology Reviewer
Harold Silver	Clinical Microbiology Reviewer
Al Sheldon, PhD	Clinical Microbiology Team Leader
Paul Buehler, PharmD, PhD	Clinical Pharmacology/Pharmacokinetics Reviewer
Joel Jiang, PhD	Biostatistical Reviewer
Susmita Samanta, MD	Regulatory Health Project Manager
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On July 15, 2003, DAIDP requested a telecon with Alcon to discuss labeling revisions. The telecon was scheduled for July 17, 2003. On July 16, 2003, DAIDP emailed to Alcon a list of discussion points to be addressed for the coming telecon (italicized within the **DISCUSSION & RECOMMENDATIONS** section).

MEETING OBJECTIVE:

To discuss labeling revisions proposed by Alcon.

DISCUSSION AND RECOMMENDATIONS:

1. *Lines 24, 28, 29, deletion of spaces within the chem formulas.*
 - Alcon agreed to the above proposed changes.

2. *Line 74, addition of the word "generally" is acceptable.*
 - The Division found the word "generally" added to the label on line 74 and find this to be acceptable. Alcon concurs.

3. *Line 113, "isolates" to replace*
 - Alcon agreed to the above proposed changes.

4. *Line 168-169, parentheses added before "This product...", and close parentheses after "...ophthalmic use."*
 - Alcon agreed to the above proposed changes.

5. *Line 200, parentheses added before "This product...", and close parentheses after "...in the eye."*
 - Alcon agreed to the above proposed changes.

6. *Line 200-215 reordering of the statements in the section "Information for Patients."*
 - Alcon agreed to the above proposed changes.

7. *Line 419 — changed to 86% (rounding error).*
 - Alcon agreed to the above proposed changes.

The sponsor asked for guidance from the Division concerning resistance claims for topical anti-infective products.

- The Division stated that in general a Sponsor would be expected to demonstrate efficacy of the product in treatment of a broad range of patients. Efficacy would also need to be demonstrated in a smaller number of well characterized and evaluable patients with drug-resistant pathogens.
- The Division stated that it is difficult to identify a specific number of patients needed for a _____ since this in part depends on the quality of the data submitted and the efficacy of the product. The Division commented that they will consider the totality of the package. The Division will evaluate the drug based on how it performs with _____ organisms. The data must include both microbiological and _____ clinically evaluable patients.

ACTION ITEMS:

The sponsor will incorporate the above revisions into the final label.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Janice Soreth, MD
Director, Division of Anti-Infective
Drug Products

Attachment: Drafted Label pages 1-18

**APPEARS THIS WAY
ON ORIGINAL**

146 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓
_____ § 552(b)(5) Draft Labeling

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

/s/

Daniel Nguyen
8/8/03 03:57:05 PM
CSO
07-17-03 Telecon

Frances LeSane
8/8/03 04:00:47 PM
CSO

Jean Mulinde
8/8/03 04:03:22 PM
MEDICAL OFFICER

Janice Soreth
8/8/03 04:41:25 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: July 15, 2003

TIME: 11:50 AM LOCATION: S-300

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

Michael Wall, PhD	Sr. Director, Otic/Nasal Product Development
Shery Dupre, BS	Assistant Director, Otic Clinical Development
Peter Conroy, PhD, JD	Associate Director, Otic/Nasal Product Development
Celeste McLean, ASCP	Scientist II, Microbiology
David W. Stroman, PhD	Director, Anti-Infective Microbiology
Leslie Lemke, PhD	Sr. Scientist, Toxicology
Shivakumar Patil, PhD	Associate Director, Clinical Pharmacology
Susan Potts, MS	Manager, Biostatistics-ENT and Anti-Infectives
Darell Turner, PhD	Sr. Director, Biostatistics & Clinical Data Management
Michael Pflieger, JD	Sr. Director, Regulatory Affairs
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs

Representing: Alcon Research Ltd. (Alcon)

AND

Name:

Janice Soreth, MD	Director, DAIDP
Jean Mulinde, MD	Medical Team Leader
Tom Smith, MD	Clinical Reviewer
Peter Kim, MD	Clinical Reviewer
Amy Ellis, PhD	Pharmacology/Toxicology Reviewer
Harold Silver	Clinical Microbiology Reviewer
Phil Colangelo, PharmD, PhD	Clinical Pharmacology/Pharmacokinetics Team Leader
Paul Buehler, PharmD, PhD	Clinical Pharmacology/Pharmacokinetics Reviewer
Daphne Lin, PhD	Biostatistical Team Leader
Susmita Samanta, MD	Regulatory Health Project Manager
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On July 13, 2003, Alcon requested a telecon with DAIDP to discuss labeling revisions. The telecon was scheduled for July 15, 2003. On the morning of July 15, 2003, Alcon emailed to DAIDP a list of discussion points to be addressed for the coming telecon (italicized within the **DISCUSSION & RECOMMENDATIONS** section).

MEETING OBJECTIVE:

To discuss labeling revisions proposed by Alcon.

DISCUSSION AND RECOMMENDATIONS:

Package Insert – Revision Teleconference Discussion Points

5

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- n
- The Division agreed to the above four proposed changes to the "Patient Information" section.

ACTION ITEMS:

The sponsor will incorporate the above revisions into the final label.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Janice Soreth
Director, Division of Anti-Infective
Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Janice Soreth
8/8/03 03:27:31 PM

APPEARS THIS WAY
ON ORIGINAL

COPY

Airborne Express Airbill Number 4340372562

July 15, 2003



Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

**RE: CIPRODEX® OTIC SUSPENSION, NDA 21-537
Amendment – CMC, Response to July 15, 2003 Facsimile**

Dear Sir/Madam:

Alcon, Inc. hereby submits an amendment to our pending application in accordance with 21 CFR 314.60.

On July 15, 2003 Alcon received a facsimile from the CMC reviewers. Alcon provides the following responses.

1. *Please revise the acceptance criteria for the boric acid assay to include [redacted] (release) and [redacted] (shelf life) of label.*

Alcon agrees to revise the acceptance criteria for the boric acid assay to include [redacted] of label at release and [redacted] of label for shelf life.

2. *We recommend an expiration period of [redacted] from evaluation of all the supporting data submitted. The results of the primary stability studies demonstrate satisfactory stability for 24 months. Under the approved protocol, Alcon may wish to extend the shelf life (via the Annual Report) in accordance with Section XI.C.1 of the November 1999 Guidance on Changes to an Approved NDA or ANDA.*

Alcon agrees to the recommended expiry period of [redacted] for Ciprodex® Otic Suspension.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,

A handwritten signature in black ink, appearing to be "Seane D. Jones", written over a horizontal line.

Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

ATTACHMENT #2:

From: Nguyen, Daniel
Sent: Monday, July 07, 2003 11:36 AM
To: 'Seane.Jones@AlconLabs.com'
Subject: NDA 21-537 (Ciprodex): Labeling Negotiations_PharmTox
Hi Seane.

The following are comments from Dr. Amy Ellis, the Pharmacology/Toxicology Reviewer. It is in response to your previous email which stated Alcon's position to the revisions made by the Pharm/Tox reviewer to your proposed label. Hopefully, this will set the stage for a productive telecon this afternoon.

Regards,
Danny

Pharmacology/Toxicology Reviewer's Comments:

Regarding the ciprofloxacin oral fertility study, we used a dose comparison based on a patient of 10 kg body weight since the product is approved for children. The exact dose multiple calculated was 141. Fertility information applies to both children and adults and the product will be labeled for use by both pediatric and adult populations. The dose multiple is still so large that we would expect it to be reassuring to a practitioner and we think it demonstrates that fertility issues would not be of concern for ciprofloxacin given by an otic route.

Regarding the dexamethasone dermal study, we propose to delete the [redacted], but leave the rest of the paragraph intact with addition of one qualifier. Keep the first 2 sentences as written and have the last sentence read "The relevance of this study for short term otic use is unknown.", deleting the rest of this sentence from " [redacted] onward.

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

/s/

Daniel Nguyen
7/23/03 09:14:00 AM
CSO
07-07-03 Telecon
Please sign off

Frances LeSane
7/23/03 11:47:54 AM
CSO

Amy Ellis
7/23/03 03:50:51 PM
PHARMACOLOGIST

MEMORANDUM OF TELECON

DATE: July 07, 2003 **TIME:** 2:00 PM **LOCATION:** S-300

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

Robert Hackett, PhD	Vice President, Product Safety
Leslie Lemke, PhD, MS	Sr. Scientist, Otic/Nasal, Toxicology
Michael Wall, PhD	Director, Otic/Nasal Product Development
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs

Representing: Alcon Research Ltd. (Alcon)

AND

Name:

Jean Mulinde, MD	Medical Team Leader
Amy Ellis, PhD	Pharmacology/Toxicology Reviewer
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On July 3, 2003, Alcon requested a telecon with DAIDP to discuss the labeling revisions suggested by the Pharmacology/Toxicology reviewer (attachment #1). The telecon was scheduled for July 7, 2003 at 2:00 PM. On the morning of July 7, 2003, DAIDP emailed to the sponsor further comments from the Pharmacology/Toxicology reviewer (attachment #2).

MEETING OBJECTIVE:

To discuss the proposed Pharmacology/Toxicology labeling revisions.

NDA # 21-537
PAGE # 2

DISCUSSION AND RECOMMENDATIONS:

The sponsor agreed with the suggested Pharmacology/Toxicology revisions in light of the comments from the Division received on the morning of July 7, 2003.

ACTION ITEMS:

The sponsor will incorporate the Pharmacology/Toxicology revisions into the proposed label.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Amy Ellis, PhD
Pharmacology/Toxicology Reviewer

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT #1:

From: Nguyen, Daniel
Sent: Thursday, July 03, 2003 11:15 AM
To: 'Seane.Jones@AlconLabs.com'
Subject: NDA 21-537 (Ciprodex): Pharm/Tox Labeling

Hi Seane,

Attached please find the proposed revisions to the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy - Teratogenic Effects, Pregnancy Category C, and Pediatric Use** subsections of the CIPRODEX Otic Suspension labeling. These comments were provided by the Pharmacology/Toxicology Reviewer.

Should you have any questions or need clarification, please do not hesitate to contact me by email or just drop me a phone call. Additional suggested revisions will be provided once they are available.

Regards,
Danny

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of CIPRODEX[®] Otic suspension have been performed to evaluate carcinogenic potential.

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 100 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with CIPRODEX[®] Otic twice per day according to label directions.

Long term studies have not been performed to evaluate the carcinogenic potential of topical otic dexamethasone. Dexamethasone has been tested for *in vitro* and *in vivo* genotoxic potential and shown to be positive in the following assays; chromosomal aberrations, sister-chromatid exchange in human lymphocytes and micronuclei and sister-chromatid exchanges in mouse bone marrow. However, the Ames/Salmonella assay, both with and without S9 mix, did not show any increase in His⁺ revertants.

The effect of dexamethasone on fertility has not been investigated following topical otic application. However, the lowest toxic dose of dexamethasone identified following topical dermal application was

1.802 mg/kg in a 26-week study in male rats and resulted in changes to the testes, epididymis, sperm duct, prostate, seminal vesicle, Cowper's gland and accessory glands. The relevance of this study for topical otic use is unknown.

Pregnancy

Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Animal reproduction studies have not been conducted with CIPRODEX[®] Otic. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when CIPRODEX[®] Otic is used by a pregnant woman.

Pediatric Use:

The safety and efficacy of CIPRODEX[®] Otic have been established in pediatric patients 6 months and older (937 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that would preclude use of this product. See DOSAGE AND ADMINISTRATION.

No clinically relevant changes in hearing function were observed in 69 pediatric patients treated with CIPRODEX[®] Otic and tested for audiometric parameters.

MEMORANDUM OF TELECON

DATE: June 30, 2003

TIME: 10:30 AM LOCATION: S-300

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

Rex Hall, PhD	Associate Director, Analytical Chemistry
Randall Kolega, PhD	Sr. Scientist II, Analytical Chemistry
Danny Dunn, PhD	Vice President, Analytical Chemistry
Haresh Bhagat, MS	Senior Director, Pharmaceuticals
Suresh Dixit, PhD	Associate Director, Formulation Dev./External Diseases
Joseph Bullock, PhD	Sr. Scientist I, Formulation Dev./External Diseases
Tom Wernet, MS	Senior Director, Technical Documentation
Sean Griffin, BS	Sr. Document Analyst, Technical Documentation
Michael Wall, PhD	Director, Otic/Nasal Product Development
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs

Representing: Alcon Research Ltd. (Alcon)

AND

Name:

Jean Mulinde, MD	Medical Team Leader
Anitra Dunson, MD	Clinical Reviewer
Jim Vidra, PhD	Chemistry Team Leader
Milton Sloan, PhD	Chemistry Reviewer
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On June 27, 2003, DAIDP requested a telecon with the sponsor to discuss chemistry stability issues. The telecon was scheduled for June 30, 2003 at 10:30 AM. In preparation for the telecon, preliminary comments, from the chemistry reviewer were faxed to the sponsor on June 29, 2003 (see attached).

MEETING OBJECTIVE:

To discuss chemistry stability issues.

NDA # 21-537

PAGE # 2

DISCUSSION AND RECOMMENDATIONS:

- The sponsor agreed to review and revise acceptance criteria in view of the updated stability data for Ciprodex.
- The sponsor agreed to revise stability protocol to include additional test and time point as stated. Accelerated conditions were agreed to not be included.

ACTION ITEMS:

The sponsor will submit the requested information when available.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Jim Vidra, PhD
Chemistry Team Leader

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Daniel Nguyen
7/23/03 01:53:57 PM
CSO
06-30-03 Telecon
Please sign off

Frances LeSane
7/24/03 04:24:39 PM
CSO

Jim Vidra
7/24/03 04:32:41 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2003

To: Seane Jones, MS, RAC	From: LT Daniel Nguyen
Company: Alcon Research, Ltd.	Division of Anti-Infective Drug Products
Fax number: 817-551-4630	Fax number: 301-827-2325
Phone number: 817-568-6296	Phone number: 301-827-2125
Subject: Chemistry Reviewer Comments	

Total no. of pages including cover: 3

Comments: Please confirm the receipt of this fax with a follow-up email to me

(nguyenda@cder.fda.gov). Thank you.

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FAXED
6-29-03
3:50 pm

NDA 21-537

Reviewer Comments

Page 1

Sponsor: Alcon Research, Ltd,

Product: Ciprodex Otic Suspension

Chemistry Comments:

1. CiproDex Otic Suspension Degradation Product -
_____ was reported at levels up to _____ of label through _____, at 25°C/40% RH and up to _____ of label through _____ at 40°C/15% RH. These levels were extrapolated to _____ of label after 24 months (two years) at 25°C/40% RH. The specification for _____ is proposed at no more than _____ of label for the shelf life of the drug product based on a maximum projected level of _____ of label.

Reviewer Comment:

Please tighten the acceptance criteria (nmt _____ of label) for the degradation product _____ to levels closer to the actual observed.

Please update the _____ stability data in the NDA. The full 24-month data should now be available in the primary stability batches to adequately support the proposed shelf life.

2. CiproDex Otic Suspension Degradation Product -
_____ was observed at levels up to _____ of label through _____ at 25°C/40% RH and up to _____ of label through _____ at 40°C/15% RH. These levels were extrapolated to _____ of label after two years at 25°C/40% RH. The acceptance criteria for _____ is proposed at no more than _____ of label for the shelf life of the drug product.

Reviewer Comment:

Please tighten the acceptance criteria (nmt _____ of label) for the degradation product _____ to levels closer to the actual observed.

Please update the _____ stability data in the NDA. The full 24-month data should now be available in the primary stability batches to adequately support the proposed shelf life.

3. Total ciprofloxacin related impurities was observed at levels up to _____ of label through _____ at 25°C/40% RH, up to _____ of label through _____ after _____ at 40°C/15% RH.

Reviewer Comment:

Please tighten the acceptance criteria (nmt _____ of label) for the total ciprofloxacin related degradation product to levels closer to the actual observed.

Please update the _____ stability data in the NDA. The full 24-month data should now be available in the primary stability batches to adequately support the proposed shelf life.

4. The dexamethasone degradation product _____ has been observed at levels up to _____ of label through _____ at 25°C/40% RH and at levels up to _____ of label through _____ at 40°C/15% RH. Based upon the observed effects of _____ formation of this degradation product, these levels have been extrapolated to _____ of label after two years at 25°C/40% RH. The specification for _____ is set at no more than _____ of label for the shelf life of the drug product.

Reviewer Comment:

Please re-examine the proposed acceptance criteria for dexamethasone related degradation product with a view toward tightened levels to reflect more closely the actual observed.

Please update the _____ stability data in the NDA. The full 24-month data should now be available in the primary stability batches to adequately support the proposed shelf life.

5. In your proposed Stability Protocol and Commitment:

Please include the additional test for weight loss/gain.

Please include accelerated storage conditions.

Please include additional time points beyond 24 months in your study design to allow for possible extension of expiry dating based on the primary batches. Testing in second year of study may be done semi-annually and thereafter annually.

**APPEARS THIS WAY
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/s/

Daniel Nguyen

7/22/03 09:42:20 AM

CSO

fax comments Chem 6-29-03

Please sign off, already faxed to sponsor back on

June 29, 2003

Frances LeSane

7/22/03 12:42:03 PM

CSO

Milton Sloan

7/22/03 01:26:39 PM

CHEMIST



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2003

To: Seane Jones, MS, RAC	From: LT Daniel Nguyen
Company: Alcon Research, Ltd.	Division of Anti-Infective Drug Products
Fax number: 817-551-4630	Fax number: 301-827-2325
Phone number: 817-568-6296	Phone number: 301-827-2125
Subject: Chemistry Reviewer Comments	

Total no. of pages including cover: 2

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FAXED
 7-15-03
 3:08 pm

NDA 21-537

Submission Dated 7-3-03

Submission Received 7-7-03

Reviewer Comments

Page 1

Sponsor: Alcon Research, Ltd.

Product: Ciprodex Otic Suspension

Chemistry Comments:

1. Please revise the acceptance criteria for the boric acid assay to include (release) and shelf life) of label.
2. We recommend an expiration period of from evaluation of all the supporting data submitted. The results of the primary stability studies demonstrate satisfactory stability for 24 months. Under the approved protocol; Alcon may wish to extend the shelf life (via the Annual Report) in accordance with Section XI.C.1 of the November 1999 Guidance on Changes to an Approved NDA or ANDA.

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/s/

Daniel Nguyen
7/15/03 03:14:00 PM
CSO
fax comments Chem 7-15-03
Please sign off

Frances LeSane
7/16/03 07:18:08 PM
CSO

Milton Sloan
7/17/03 09:18:39 AM
CHEMIST



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: June 13, 2003

To: Seane Jones, MS, RAC	From: LT Daniel Nguyen
Company: Alcon Research, Ltd.	Division of Anti-Infective Drug Products
Fax number: 817-551-4630	Fax number: 301-827-2325
Phone number: 817-568-6296	Phone number: 301-827-2125

Subject: Micro request for information.

Total no. of pages including cover: 3

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FAXED
 6-13-03

12:25 pm

NDA 21-537

Reviewer Comments

Page 1

Sponsor: Alcon Research, Ltd.

Product: Ciprodex Otic Suspension

Microbiology Comments:

To aid in the review of the NDA 21-537, please provide the following described clinical/bacteriological line listing tables for each indication:

Presentation of Data:

- Separate tables by AOMT and AOE indications,
- Separate tables for each of the pivotal protocols (i.e., #C-00-52, C-99-59 and C-98-18, C-98-19), respectively,
- Separate tables for the MITT and MPP populations,
- Combine the aforementioned population tables into 2-Summary tables (MITT & MPP).
- Use revised MITT and MPP populations from May 5, 2003 submission.

Overall Data:

- All organisms are to be speciated in each table,
- Group all organisms of the same species together.

Example AOMT or AOE Clinical/Micro Line Listing Table Format

Study Protocol Number and Title

Investigator:

<u>Patient ID</u>	<u>Visit Day</u>	<u>Targeted Organisms Isolated</u>	<u>CIPRODEX MIC Disc</u>	<u>Comparator MIC Disc</u>	<u>Clinical Outcome</u>	<u>Bacteriological Outcome</u>
-------------------	------------------	------------------------------------	--------------------------	----------------------------	-------------------------	--------------------------------

MIC = µg/mL
Disk = mm

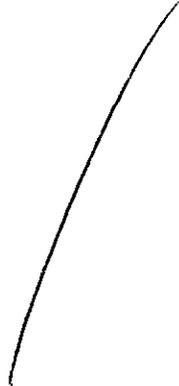
NDA 21-537

Reviewer Comments

Page 2

Sponsor: Alcon Research, Ltd.

Product: Ciprodex Otic Suspension



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/s/

Daniel Nguyen
6/13/03 12:24:24 PM
CSO
fax comments micro 6-13-03

Frances LeSane
6/17/03 10:52:32 AM
CSO

Harold Silver
6/17/03 03:00:09 PM
MICROBIOLOGIST

**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: June 12, 2003 TIME: 02:30 PM LOCATION: S-333

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

Celeste McLean, ASCP	Microbiologist
David Stroman, PhD	Microbiologist
Michael Pfleger, JD	Senior Director, Regulatory Affairs
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs

Representing: Alcon Research Ltd. (Alcon)

AND

Name:

Harold V. Silver	Clinical Microbiology Reviewer
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On June 11, 2003, DAIDP requested a telecon with the sponsor to discuss microbiology issues. The telecon was scheduled for June 12, 2003 at 2:30 PM.

MEETING OBJECTIVE:

To request additional clinical microbiology information.

NDA # 21-537

PAGE # 7

DISCUSSION AND RECOMMENDATIONS:

The sponsor agreed to provide the Division with the additional information as listed under "ACTION ITEMS".

ACTION ITEMS:

The sponsor will submit microbiology line listing tables in the following format:

- Separate tables by AOMT and AOE indications.
- Separate tables for each of the pivotal protocols (i.e., #C-00-52, C-99-59 and C-98-18, C-98-19), respectively.
- Separate tables for the MITT and MPP populations.
- Combine the aforementioned population tables into 2-Summary tables (MITT & MPP). Use revised MITT and MPP populations from May 5, 2003 submission.

The sponsor will submit this additional information by June 24, 2002.

An example of the line listing tables requested will be faxed to the sponsor.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Harold V. Silver
Clinical Microbiology Reviewer

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/s/

Daniel Nguyen
7/9/03 09:10:31 AM
CSO
06-12-03 Telecon
Please sign off.

Frances LeSane
7/9/03 06:53:10 PM
CSO

Harold Silver
7/9/03 07:51:30 PM
MICROBIOLOGIST

Please sign off.

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July 3, 2003

Alcon
RESEARCH, Ltd.

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

RE: CIPRODEX® OTIC SUSPENSION, NDA 21-537
Amendment – CMC, Response to June 30, 2003 Teleconference

Dear Sir/Madam:

Alcon, Inc. hereby submits an amendment in accordance with 21 CFR 314.60.

On June 30, 2003 Alcon and FDA Chemists held a teleconference to discuss the tightening of specifications for our product under review, Ciprodex® Otic Suspension.

Alcon has reviewed the stability data for all primary stability batches. Following the discussion with FDA, the limits of specification have been reviewed with the intent to further tighten the limits where applicable. The revisions are based on the statistical analysis of real time primary stability data and projection for the shelf life for the trade package sizes.

Provided in this amendment are our revised specifications, post approval stability protocol, stability commitment and updated stability data.

A copy of this supplement is being submitted simultaneously to our Dallas District office.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

ORIG AMENDMENT

N'000/BT

Alison
RESEARCH, INC.

Airborne Express Airbill Number 4340371965

June 24, 2003

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

RECEIVED

JUN 25 2003

MEGA/CDER

RE: CIPRODEX® OTIC SUSPENSION, NDA 21-537
General Correspondence – June 12, 2003 Teleconference Response With
Patient Listings for AOMT/AOE and ————— for AOMT/AOE

Dear Sir/Madam:

Provided in this submission are the following Microbiological / Biostat tables as agreed upon in our June 12, 2003 teleconference with FDA team members Dr. Harold Silver and Lt. Daniel Nguyen.

- Acute Otitis Media ————— tympanostomy tube ————— major pathogens, MITT and MPP datasets.
- Acute Otitis Media with Otorrhea through tympanostomy tube patient listing for major pathogens – all specimens, MITT and MPP datasets.
- Acute Otitis Externa ————— major pathogens, MITT and MPP datasets.
- Acute Otitis Externa patient listing for major pathogens – all specimens, MITT and MPP datasets.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,


Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

ORIGINAL

N.000(E2)

ORIG AMENDMENT

Airborne Express Airbill Number 4340371862

May 30, 2003

RECEIVED

JUN 02 2003

MEGA/CDER

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: CIPRODEX® OTIC SUSPENSION, NDA 21-537
General Correspondence – May 23, 2003 Teleconference Response With Biostat Report

Dear Sir/Madam:

Provided in this submission are the following Biostat Reports as agreed upon in our May 23, 2003 teleconference with FDA.

- Updated patient accounting tables.
- Isolate level patients who were excluded from MRP analyses because of reinfection, superinfection, sterile exit culture, etc., and
- SAS transport file differences between original data files and data files provided for Biostatistics Report pc1582.05.

In addition, an error was discovered in fulfilling request #2, above. It was noted that the microbiological outcome classification was incorrect in the original data set for 2 patients in Study C-98-19. This error did not affect the patient level outcomes, but it did cause them to be erroneously excluded from the isolate level analyses of the MPP data set. This affected 2 tables from the Biostatistics Report pc1582.05 which have now been corrected and provided in this report.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,


Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

ORIGINAL

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

MEMORANDUM OF TELECON

DATE: May 23, 2003 TIME: 11:00 AM LOCATION: S-346

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

Celeste McLean, ASCP	Scientist II Microbiologist
Allen Epp	Senior SAS Programmer II, Biostatistics
Sheryl Dupre, BS	Assistant Director, Otic Clinical Development
Susan Potts, MS	Manager, Biostatistics & Clinical Data Management
Darell Turner, PhD	Senior Director, Biostatistics & Clinical Data Management
Peter Conroy, PhD, JD	Associate Director, Clinical Science
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs

Representing: Alcon Research Ltd. (Alcon)

AND

Name:

Jean Mulinde, MD	Medical Team Leader
Tom Smith, MD	Clinical Reviewer
Joel Jiang, PhD	Biostatistical Reviewer
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On April 4, 2003 DAIDP sent Alcon a facsimile requesting that the sponsor conduct some additional biostatistical analyses. On May 6, 2003 the sponsor submitted the requested information.

MEETING OBJECTIVE:

To request additional information on the biostatistical analyses submitted on May 6, 2003.

NDA #21-537

PAGE # 2

DISCUSSION AND RECOMMENDATIONS:

The sponsor agreed to provide the Division with the additional information as listed under "ACTION ITEMS".

ACTION ITEMS:

The sponsor will submit the following regarding the biostatistical analyses submitted on May 6, 2003:

- The sponsor will provide Accounting Tables for the revised data sets from all four studies.
- The sponsor will provide listings of patients in each of the four studies who were excluded from the analyses because of reinfection or superinfection.
- The sponsor will provide names and definitions for the variables that were added to the new SAS transport data sets.

The sponsor will submit this additional information within two weeks from this telecon.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Jean Mulinde, MD
Medical Team Leader

**APPEARS THIS WAY
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/s/

Daniel Nguyen
6/17/03 10:27:04 AM
CSO
05-23-03 Telecon

Frances LeSane
6/17/03 10:59:38 AM
CSO

Jean Mulinde
6/18/03 10:29:20 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

Airborne Express Airbill Number 4340371663

May 5, 2003

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

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MAY 06 2003

MEGA/ODER

RE: CIPRODEX® OTIC SUSPENSION, NDA 21-537
General Correspondence – Request for Additional Info/Analysis From
Clinical and Biostatistical Reviewers

N-000(B2)

Dear Sir/Madam:

ORIGINAL AMENDMENT

Provided are additional analyses and information as requested in your April 4, 2003 facsimile.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

ORIGINAL

Airborne Express Airbill Number 4340374161

April 29, 2003

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APR 30 2003

MEGA/CDER

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
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Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-0099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

**RE: CIPRODEX® OTIC SUSPENSION, NDA 21-537
General Correspondence – Patient Case Report Forms**

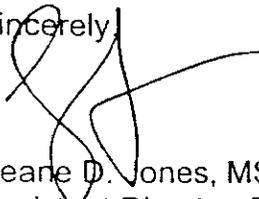
Dear Sir/Madam:

As per your April 28, 2003 request, the following 7 patient case report forms from clinical study C-00-52 are provided.

- 2702
- 2712
- 2713
- 2714
- 2739
- 2741
- 2742

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

ORIGINAL

ROWS	INV	PAT	SEX	BIRTHDATE	RACE	RACE_OTHER	AGE	EAR	otomrhea_cess	otomrhea_end	duration_night	duration_left
1	2			2	15280 E	E		3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
2	2		3 687825e-40		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
3	2		2		60 A			1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
4								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
5								1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
6								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
7								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	0
8								-1 240158e69	-1 754082e69	-1 240158e69	-1 240158e69	0
9								-1 240158e69	-1 754082e69	0	1 755767e69	1 240158e69
10					1		0	0	1 240158e69	0	-1 755767e69	-1 754082e69
11	0		0		1 AC			-1 757452e69	-1 240158e69	-1 754082e69	0	0
12					A			-1 240158e69	-1 240158e69	1 240158e69	1 240158e69	-1 240158e69
13	3419		2		687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	5 280541e-40	1 551812e-78
14			3 687825e-40		3 687825e-40			4 844365e66	4 844365e66	4 844365e66	4 844365e66	6 851881e66
15								3 671676e-18	2 277658e-78	2 194886e-78	2 301258e-78	2 194886e-78
16	1		771 01298739		3 858463e66		0	3 687825e-40	3 687825e-40	6 851881e66	6 891373e66	6 858463e66
17	2		3 687825e-40		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
18	2				60 A			-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
19	1							-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
20								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
21								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
22								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
23								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 754082e69
24								-1 240158e69	-1 755767e69	-1 757452e69	-1 839461e69	-1 754082e69
25								-1 240158e69	0	0	0	-1 240158e69
26					1		0	-1 755767e69	-1 240158e69	-1 754082e69	-1 755767e69	-1 754082e69
27	0		0		1 AC			-1 757452e69	-1 240158e69	-1 755767e69	0	0
28	3				0			-8 661015e68	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
29			2		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	5 280541e-40	1 551812e-78
30			3 687825e-40		3 687825e-40		0	-1 321546e64	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
31			3 687825e-40		3 687825e-40			-4 844365e66	-4 844365e66	-4 844365e66	-4 844365e66	-6 851881e66
32	0							-1 755767e69	-1 240158e69	-1 811391e69	3 671729e-18	2 284157e-78
33								3 671729e-18	2 284173e-78	2 194886e-78	2 300679e-78	2 209645e-78
34						C0052C*@	0	2 301425e-78	2 194886e-78	1 083754e-78	3 687825e-40	3 687825e-40
35	2		3 687825e-40		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
36	2		2		60 A			-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
37	2							-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
38								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
39								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
40								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
41								-1 240158e69	1 240158e69	-1 240158e69	-1 240158e69	-1 754082e69
42								-1 240158e69	-1 754082e69	-1 240158e69	-1 240158e69	-1 754082e69
43								-1 240158e69	-1 754082e69	0	-1 754082e69	-1 240158e69
44					1 AP		0	-1 755767e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 755767e69
45								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
46					A			-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
47	15054		1		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	5 280541e-40	1 551812e-78
48			3 687825e-40		3 687825e-40			-4 844365e66	-4 844365e66	-4 844365e66	-4 844365e66	-6 851881e66
49	0							-1 754082e69	-1 240158e69	-1 811391e69	3 671848e-18	2 292582e-78
50						C0052C*D	0	2 301083e-78	2 194886e-78	1 083754e-78	3 687825e-40	3 687825e-40
51	1		771 01298739		-6 858463e66		0	3 687825e-40	3 687825e-40	-6 851881e66	-6 878209e66	-6 858463e66
52	2		3		15314 E	E		3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
53	2		3 687825e-40		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
54	2		2		60 A			-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
55	3							-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
56								-1 240158e69	-1 240158e69	1 240158e69	-1 240158e69	-1 240158e69
57								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
58								-1 240158e69	-1 240158e69	1 240158e69	-1 240158e69	-1 240158e69
59								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 754082e69
60								-1 240158e69	-1 754082e69	-1 240158e69	-1 240158e69	0
61								-1 240158e69	0	0	0	-1 240158e69
62					1		0	0	1 240158e69	0	1 755767e69	-1 754082e69
63								-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69
64	4		2		0			8 661015e68	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
65								3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
66					1 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	3 694047e-40	8 127496e73
67	15378		2		2 353082e-19	chia coli	0	3 687825e-40	3 687825e-40	3 687825e-40	7 832954e-40	2 207536e-78
68			3 687825e-40		3 687825e-40		0	-1 321546e64	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
69			3 687825e-40		3 687825e-40			-4 844365e66	-4 844365e66	-4 844365e66	-4 844365e66	-4 844365e66
70								3 66167e-18	2 29671e-78	2 196994e-78	2 30165e-78	2 194886e-78
71						C0052C*E	0	2 299957e-78	2 194886e-78	1 083754e-78	3 687825e-40	3 687825e-40
72	2		2		15044 E	7		3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
73	2		3 687825e-40		3 687825e-40		0	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40	3 687825e-40
74	2		2		60 A			-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69	-1 240158e69

Rows	INV	PAT	EAR_SEQ	TMT	TRE	COMPLETE_STUDY	EXTERNAL_DISC	REASON_OTHER_TXT
1	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A0
2				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
3	2			3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
4				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
		A		-4.507703e71	-3.174803e71	-4.645555e71	2.3703284e22	IIC A0
		A		-3.174803e71	-4.490449e71	-4.490449e71	-6.161244e71	819C A
7		A		0	-4.490449e71	-4.490449e71	0	
8				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A
9				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
10	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
11	2	AP		-3.174803e71	-4.494762e71	-4.520644e71	-3.174803e71	
12		HHPg		0	-4.490449e71	-6.161244e71	4.476868e-11	
13				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
14	2			-4.494762e71	-4.490449e71	-4.494762e71	-4.490449e71	
15	2			3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
16				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A0
17	5	A		-4.563241e71	-3.174803e71	-5.821542e71	3.4283873e17	A0
18				-3.174803e71	-3.174803e71	-4.490449e71	-4.989216e71	
19	0			0	-4.490449e71	-4.490449e71	0	
20				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
21		HHuQ		0	-4.490449e71	-6.161244e71	4.476868e-11	
22				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
23	2			-4.494762e71	-4.490449e71	-4.490449e71	-4.490449e71	
24	2			3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
25	10	COLY		1.5703284e15	3.687825e-40	3.687825e-40	3.687825e-40	A
26		A		-3.174803e71	-4.490449e71	-4.490449e71	-6.161244e71	819Cp
27	0			0	-4.490449e71	-4.490449e71	0	
28	1	A		-3.174803e71	-3.174803e71	-3.174803e71	-2.21722e+71	A
29				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
30	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
31	2	A		-4.490449e71	-3.174803e71	-3.174803e71	-3.174803e71	
32		HH01E		0	-4.490449e71	-6.161244e71	4.476868e-11	
33				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
34	2			-4.494762e71	-4.494762e71	-4.494762e71	-4.490449e71	
35	2			3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
36				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
		A		-3.174803e71	-4.490449e71	-4.490449e71	-6.161244e71	819CYP
				0	-4.490449e71	-4.490449e71	0	
39				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A
40	2			-4.490449e71	-4.49076e71	-4.490449e71	-2.21722e+71	A
41				-4.490449e71	-4.988886e71	0	-4.490449e71	
42				-3.174803e71	-3.174803e71	-3.174803e71	-3.174803e71	
43	2	A		-3.174803e71	-3.174803e71	-3.174803e71	-2.21722e+71	A
44				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A
45				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
46	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
47	2			-4.494762e71	-4.51633e+71	-4.490449e71	-2.21722e+71	A0
48				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
49	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
50	2	A		-3.174803e71	-3.174803e71	-3.174803e71	-2.21722e+71	A0
51				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A
52				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
53	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
54	5	A		-4.503389e71	-4.490449e71	-2.21722e+71	3.687825e-40	A
55				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
56	2	A0		-4.490449e71	-3.174803e71	-3.174803e71	-3.174803e71	
57				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
58				-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
59				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A
60		A@		-4.51633e+71	-3.174803e71	-5.821542e71	3.4283873e17	A
61				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A0
62				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A0
63				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
64	3			-4.494762e71	-4.51633e+71	-3.174803e71	-4.645555e71	SPORIN A
65				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A0
66		A		-4.51633e+71	-4.490449e71	-2.21722e+71	3.687825e-40	A
67				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
68	2	A		-4.490449e71	-3.174803e71	-3.174803e71	-3.174803e71	
9	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A
70	1	A		-3.174803e71	-3.174803e71	-3.174803e71	-2.21722e+71	A
71				-2.21722e+71	3.687825e-40	3.687825e-40	3.687825e-40	A
72				3.687825e-40	3.687825e-40	3.687825e-40	3.687825e-40	A
73	2	Ap		-3.174803e71	-4.490449e71	-4.529271e71	-4.490449e71	
74	1			-3.174803e71	-2.21722e+71	3.687825e-40	3.687825e-40	A

Ciprodex Otic Suspension (NDA21-537)

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Study C9818

Random Sample of Patients in Each Treatment Arm

Obs	PAT	INV
1	4008	2517
2	4009	2517
3	4011	2517
4	4013	2517
5	4015	2517
6	4017	2517
7	4019	2517
8	4021	2517
9	4203	2272
10	4306	2090
11	4307	2090
12	4311	2090
13	4325	2090
14	4402	2507
15	4404	2507
16	4405	2507
17	4407	2507
18	4411	2507
19	5111	2210
20	5112	2210
21	5124	2210
22	5801	2404
23	5804	2404
24	5821	2404
25	6206	2280
26	6207	2280
27	6304	2328
28	6805	2223
29	6808	2223
30	6823	2223
31	6836	2223
32	6837	2223
33	7009	2356
34	7010	2356
35	7012	2356
36	7025	2356
37	7033	2356
38	7035	2356
39	7207	2397
40	7209	2397
41	7211	2397
42	7301	2358
43	7304	2358
44	7306	2358
45	7308	2358
46	7314	2358
47	7403	2274

48	7405	2274
49	7406	2274
50	7411	2274
51	7501	2286
52	7503	2286
53	7505	2286
54	7606	2367
55	7607	2367
56	7613	2367
57	7614	2367
58	7616	2367
59	7620	2367
60	7623	2367
61	7630	2367
62	7631	2367
63	7637	2367
64	7639	2367
65	7641	2367
66	7806	2414
67	7809	2414
68	7815	2414
69	7817	2414
70	8020	2371
71	8030	2371
72	8039	2371
73	9315	2451
74	9316	2451

Study C9818

Random Sample of Patients in Each Treatment Arm

Obs	PAT	INV
75	9321	2451
76	9323	2451
77	9330	2451
78	9404	2424
79	9718	2471
80	9721	2471
81	9811	2475
82	9825	2475
83	9828	2475
84	9830	2475
85	9840	2475
86	9841	2475
87	9901	2502
88	9903	2502
89	9904	2502
90	9914	2502
91	9917	2502
92	9919	2502

Ciprodex Otic Suspension (NDA21-537)

1

Study C9819

Random Sample of Patients in Each Treatment Arm

Obs	PAT	INV
1	1001	2212
2	1102	2381
3	1306	2365
4	1308	2365
5	1309	2365
6	1311	2365
7	1313	2365
8	1315	2365
9	1707	2284
10	1709	2284
11	1710	2284
12	1712	2284
13	1724	2284
14	1725	2284
15	1727	2284
16	1729	2284
17	1811	2362
18	1812	2362
19	1906	2398
20	1907	2398
21	2017	2271
22	2101	1689
23	2106	1689
24	2110	1689
25	2207	2395
26	2211	2395
27	2505	2228
28	2511	2228
29	2818	2332
30	2823	2332
31	2904	2359
32	2905	2359
33	2911	2359
34	2914	2359
35	2916	2359
36	2923	2359
37	2930	2359
38	2932	2359
39	2938	2359
40	3002	2234
41	3003	2234
42	3007	2234
43	3010	2234
44	3014	2234
45	3018	2234
46	3020	2234
47	3022	2234

48	3032	2234
49	3034	2234
50	3036	2234
51	3108	2400
52	3109	2400
53	3110	2400
54	3114	2400
55	3120	2400
56	3304	2360
57	3306	2360
58	3307	2360
59	3315	2360
60	3513	2549
61	3521	2549

Ciprodex Otic Suspension (NDA21-537)

1

Study C9959

Random Sample of Patients in Each Treatment Arm

Obs	PAT	INV
1	1001	2138
2	1002	2138
3	1003	2138
4	1004	2138
5	1201	2228
6	1203	2228
7	1204	2228
8	1206	2228
9	1209	2228
10	1211	2228
11	1309	2280
12	1310	2280
13	1311	2280
14	1312	2280
15	1313	2280
16	1314	2280
17	1315	2280
18	1316	2280
19	1401	2287
20	1404	2287
21	1605	2612
22	1606	2612
23	1607	2612
24	1802	2807
25	1805	2807
26	1813	2807
27	1814	2807
28	1817	2807
29	1818	2807
30	2001	2829
31	2004	2829
32	2008	2829
33	2105	2830
34	2107	2830
35	2111	2830
36	2113	2830
37	2114	2830
38	2115	2830
39	2201	2839
40	2205	2839
41	2302	2842
42	2304	2842
43	2309	2842
44	2318	2842
45	2319	2842
46	2320	2842
47	2325	2842

48	2328	2842
49	2330	2842
50	2505	2884
51	2608	2890
52	2613	2890
53	2618	2890
54	2624	2890
55	2625	2890
56	2628	2890
57	2705	2900
58	2706	2900
59	2707	2900
60	3004	2956
61	3008	2956
62	3102	2957

Ciprodex Otic Suspension (NDA21-537)

1

Study C0052

Random Sample of Patients in Each Treatment Arm

Obs	PAT	INV
1	1301	2986
2	1302	2986
3	1305	2986
4	1306	2986
5	1309	2986
6	1310	2986
7	2001	2991
8	2002	2991
9	2015	2991
10	2016	2991
11	2019	2991
12	2020	2991
13	2041	2991
14	2042	2991
15	2220	3027
16	2222	3027
17	2715	2995
18	2724	2995
19	2757	2995
20	2902	2996
21	2914	2996
22	3003	2506
23	3004	2506
24	3013	2506
25	3019	2506
26	3030	2506
27	3031	2506
28	3035	2506
29	3037	2506
30	3042	2506
31	3046	2506
32	3047	2506
33	3050	2506
34	3101	2997
35	3102	2997
36	3103	2997
37	3204	2998
38	3401	3000
39	3402	3000
40	3405	3000
41	3412	3000
42	3602	3015
43	3901	3005
44	3903	3005
45	3909	3005
46	3912	3005
47	3952	3005

48	4202	3008
49	4610	3011
50	4613	3011
51	4619	3011
52	4623	3011
53	5401	3181
54	5503	3167
55	5504	3167
56	5602	3293
57	5606	3293
58	5901	3297
59	6101	3446
60	6102	3446
61	6105	3446

4 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: December 3, 2002

DUE DATE: March 30, 2003

ODS CONSULT #: 02-0216

TO: Janice Soreth
Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH: Daniel Nguyen
Project Manager
HFD-520

PRODUCT NAME:
Ciprodex
(Ciprofloxacin and Dexamethasone Otic Suspension) 0.3%/0.1%

NDA SPONSOR:
Alcon Inc.

NDA: 21-537

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Infective Drug Products (HFD-520), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Ciprodex" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS has no objections to the use of the proprietary name Ciprodex.
- 2.

In addition, to the labeling revisions outlined in Section III of this review, the Ciprodex labels and labeling should be clearly distinguished from other Alcon ophthalmic and otic products using contrasting design, color, boxing, or some other means.

3. DDMAC finds the proprietary name Ciprodex acceptable from a promotional perspective.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling 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 and established names from this date forward.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 9, 2003
NDA#: 21-537
NAME OF DRUG: Ciprodex
(Ciprofloxacin and Dexamethasone Otic Suspension) 0.3%/0.1%
NDA HOLDER: Alcon Inc

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective Drug Products, to review the proprietary name Ciprodex, regarding potential name confusion with other proprietary/established drug names. The container labels, carton and package insert labeling were reviewed for possible interventions to minimize medication errors.

PRODUCT INFORMATION

Ciprodex (ciprofloxacin and dexamethasone) Otic Suspension is an antibiotic and steroid combination indicated for the treatment of infections caused by susceptible organisms. The recommended dose of Ciprodex for Acute Otitis Media and Acute Otitis Externa (in patients older than six months of age) is 4 drops instilled into the affected ear two times a day for seven days. Ciprodex will be marketed in 5 mL and 7.5 mL DROP-TAINER dispensers.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts¹ as well as several FDA databases² for existing drug names which sound-alike or look-alike to "Ciprodex" 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.³ The Saegis⁴ Pharma-In-Use

¹ Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, Mo. <http://www.efactsweb.com/index.asp>
MICROMEDEX Integrated Index, 003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2003).

² The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

³ WWW location <http://www.uspto.gov/main/trademarks.htm>

⁴ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS 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

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Ciprodex." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS' Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified Carbodex DM and _____ as having the potential for confusion with "Ciprodex." These products are listed in Table 1 (see below and on Page 4), along with the dosage forms available and usual dosage.
2. The Expert Panel also noted that during the proprietary name review for _____ Cipro HC, Codeprex, and Casodex were reviewed as potential sound and/or look-alike names. DMETS determined that the potential for medication errors due to name confusion between Ciprodex and Cipro HC, Codeprex, or Casodex was minimal. This _____ would have no impact on the prior assessment.
3. Through independent review, DMETS also identified Repronex, Aciphex, and Cerebyx as having the potential for confusion with "Ciprodex." These products are listed in Table 1 (see below and on Page 4).
4. DDMAC did not have concerns about the name Ciprodex with regard to promotional claims.

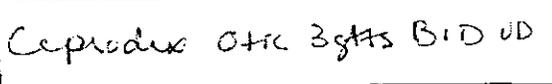
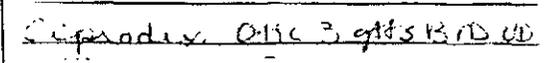
Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Ciprodex	Ciprofloxacin and Dexamethasone Otic Suspension	Four drops in affected(s) ear two times a day for seven days	N/A
Carbodex DM	Brompheniramine 4 mg and Pseudoephedrine HCl 45 mg and Dextromethorphan HBr 15 mg per 5mL Syrup	5 mL four times a day	SA
Repronex	Menotropins (HMG) 75 IU per vial	Anovulation: 75 IU daily SQ/IM for 5 days IVF Induction: 225 IU daily SQ/IM for 12 days (maximum)	LA SA
Aciphex	Rabeprazole 20 mg Tablets	20 mg to 60 mg per day depending upon indication of use (Maximum adult dose 120 mg/day)	SA

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Ciprodex	Ciprofloxacin and Dexamethasone Otic Suspension	Four drops in affected(s) ear two times a day for seven days	N/A
Cerebyx	Fosphenytoin Sodium 75 mg per mL Injection	<i>Loading doses:</i> 10 mg to 20 mg (PE) per kg IV/IM <i>Maintenance dose:</i> 4 mg to 6 mg (PE) per kg IV or IM per day. {PE=phenytoin equivalent} Depending upon indication of use	SA
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike) *** Pending Approval			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Ciprodex with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 104 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Ciprodex (see below). These prescriptions were optically scanned and one prescription was 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: 	...The first is for Ciprodex Otic Suspension 3 drops twice daily as directed. Dispense One.
Inpatient RX: 	

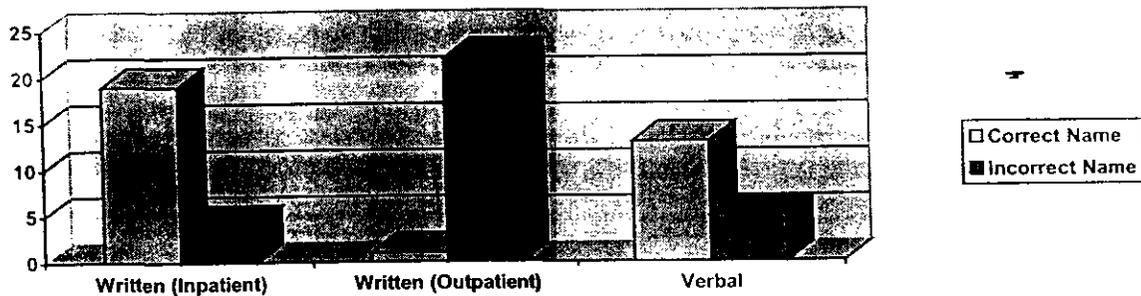
**APPEARS THIS WAY
ON ORIGINAL**

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Inpatient	39	23 (59%)	19 (83%)	4 (17%)
Written Outpatient	33	23 (76%)	1 (4%)	22 (96%)
Verbal	32	18 (56%)	13 (72%)	5 (26%)
- Total	104	64 (62%)	33 (52%)	31 (49%)



In the verbal study 5 of 18 (26%) participants interpreted "Ciprodex" incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Ciprodex." These include Cipradex (2), Cipravox (1), Cipridex (1), and Procipedex (1). None of the misinterpreted names were similar to an approved product.

Among the two written studies, 26 of 46 (57%) participants interpreted the name incorrectly. The majority of the misinterpretations included: Ciprodix (1), Ceprodix (2), and Ceprodux (2), Cipradex (3), and Ceprodex (18). None of the misinterpreted names were similar to an approved product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Ciprodex, the primary concerns raised were related to sound and/or look-alike names that currently exist in the US market: Carbodex DM, Repronex, Aciphex, and Cerebryx.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Ciprodex could be confused with Carbodex DM, Repronex, Aciphex, and Cerebryx. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name Ciprodex.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. Sound-Alike and Look-Alike Names

Carbodex DM and Ciprodex may sound alike depending upon how they are pronounced. Carbodex is a combination antihistamine, cough suppressant, and decongestant product. Both names share the same first letters (C) and the last four letters (odex). However, the first syllables of both names are distinct when pronounced 'Car' vs. 'Ci,' especially since the 'C' sound in Carbodex is pronounced using a 'k' sound. Additionally, when the 'DM' modifier is used the similarity decreases. The products have different routes of administration (oral vs. ophthalmic), dosing intervals (BID vs. QID), and dosage forms (syrup vs. suspension). Carbodex DM is usually prescribed in milliliters whereas Ciprodex is prescribed in drops. The two dosing increments do not overlap (5 mL vs. 4 drops). The differences in the beginnings of each name help to minimize the potential name confusion between Carbodex DM and Ciprodex.

Repronex and Ciprodex have sound and look-alike characteristics (see Page 7). Repronex is indicated for the treatment of infertility in women. The second syllable of both names contains the same letters (pro) and two letters in the last syllables are the same (ex). This contributes to the look and sound-alike similarities. However, the beginning sound of each name is phonetically different when pronounced (Re vs. Ci), which decreases the sound-alike similarities. When scripted Ciprodex contains an upstroke (the letter d) in the last syllable whereas Repronex does not. This upstroke helps to distinguish the two names when scripted. Differences between the two products include the route of administration (intramuscular or subcutaneous vs. ophthalmic), dosing interval (daily vs. twice daily), and dosage form (injectable vs. suspension). Repronex is marketed in two strengths (75 IU and 150 IU) whereas Ciprodex is a combination product marketed in a single strength. Thus prescribers would need to specify the strength on Repronex prescriptions. In contrast, Ciprodex prescriptions may be written without indicating a strength. The prescriber population for

Repronex will usually be *in vitro* fertilization specialists whereas prescribers of Ciprodex will include general practitioners, family practice physicians, nurse practitioners, or pediatricians. The labeling for Repronex states 'Repronex is a drug that should only be used by physicians who are thoroughly familiar with infertility problems.' Additionally, Repronex is an expensive drug, which may not be stocked in most pharmacies. Overall the product differences and conditions of use will help to minimize name confusion between Repronex and Ciprodex.

REPRONEX

CIPRODEX

repronex *ciprodex*

Aciphex and Ciprodex may look alike when scripted (see below). Aciphex is indicated for the treatment of gastroesophageal reflux disease (GERD) and Zollinger Ellison syndrome. Depending upon how the letters A and C are written they may look alike. Additionally, both names end in the same letters 'ex.' These characteristics contribute to the look-alike similarities of the two names. However, the upstrokes and downstrokes of the two names appear in different positions. With Aciphex, the upstrokes and downstrokes are next to each other and are a part of the same syllable. The upstrokes and downstrokes in Ciprodex aren't in close proximity to each other and are in different syllables. Although, a scripted 'A' can and has been misinterpreted as a 'C', the placement of the upstrokes and downstrokes in each name help to distinguish them when scripted. There are additional differences between the two products. They have different routes of administration (oral vs. otic), dosage forms (tablet vs. suspension), and most likely would not be stored near each other on pharmacy shelves. Both Aciphex and Ciprodex are marketed in single strengths and thus may be prescribed without listing a strength. Although Aciphex is available in a single strength and is usually prescribed as a 20 mg dose, the dose may be more than 20 mg per day. Therefore, prescriptions may contain a strength when written. In an outpatient setting, if a prescription for 'Ciprodex UD' was misinterpreted as 'Aciphex UD' the quantity to be dispensed would help to distinguish the two products (i.e., Ciprodex quantities include 5 mL, 7.5 mL, #1 whereas Aciphex would usually be a multiple of 30). In the inpatient setting it is less likely that 'UD' directions would be used because the nursing staff would need specific instructions to enter on the medication administration record. The differences in two names and the product differences will help to minimize the potential for name confusion between Aciphex and Ciprodex.

ACIPHEX

CIPRODEX

Aciphex *Ciprodex*

Cerebyx and Ciprodex may sound alike depending upon how they are pronounced. Cerebyx is indicated for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery. The beginnings and endings of each name sound similar (Ce vs. Ci and byx vs. dex). However, the second syllables of the names are distinct when pronounced. The 'pro' sound of Ciprodex is phonetically different than the 're' of Cerebyx. There are additional differences, which help distinguish the two names. The route of administration (intravenous or intramuscularly vs. ophthalmic), dosage forms (injection vs. suspension), and the products most likely would not be stored near each other on pharmacy shelves. Prescriptions for Cerebyx will generally require that a strength be noted whereas Ciprodex will be marketed in a single strength which can be omitted on prescriptions. Additionally, there is no overlap in strength. The phonetic differences in the second syllable of both names and the differences in the strengths will help to minimize the potential for name confusion between Cerebyx and Ciprodex.

2. Packaging Related Safety Issues

Although, DMETS had no objections to the use of the name [redacted], DMETS has received post-marketing reports associated with medication errors due to confusion among the various ophthalmic products currently manufactured by Alcon and its affiliate Falcon. The packaging configuration (e.g., carton appearance) of the various ophthalmic products is similar and has resulted in medication errors. Overall, the potential for medication errors due to selection errors may increase due to availability of [redacted] containing ciprofloxacin (Otics: Cipro HC and and Ophthalmics: Ciloxan [redacted] that are manufactured by Alcon.

Moreover, ophthalmic and otic products may be stored in close proximity to each other when stored alphabetically by proprietary/established name which may also increase selection errors.

All of these factors increase the potential of medication errors due to selection errors with Ciprodex.

DMETS' conducted a search of the Adverse Event Reporting System (AERS) database to determine if any reports of medication errors due to either name confusion or selection errors have occurred between otic and ophthalmic products containing ciprofloxacin. AERS was also searched for any reports relating to medication errors between another ophthalmic and otic product that share the same proprietary name (i.e., Cortisporin). The AERS search revealed one case (ISR# 3760238-3-00-01) where a prescriber ordered the generic version of Cortisporin Ophthalmic but the patient received generic Cortisporin Otic. No outcome information was provided. The Drug Quality Reporting System (DQRS) was also searched for any reports associated with Cortisporin Ophthalmic or Cortisporin Otic. The DQRS search did not identify any additional cases. However, there are anecdotal reports of

pharmacists confusing Cortisporin Ophthalmic Suspension, Cortisporin Otic Suspension, and Cortisporin Otic Solution. The consequences of a patient receiving an ophthalmic product in lieu of the otic product may not be severe if the active ingredients are the same. However, a patient who receives an otic product in lieu of an ophthalmic product (even if both contain the same active ingredients) may experience ophthalmic irritation or other severe ophthalmic problems. Additionally, these adverse events could have serious outcomes if the administered product also contains a corticosteroid, but the prescribed product contains only ciprofloxacin.

During the launch of Ciprodex Otic, the potential for medication errors due to name confusion may increase because practitioners are unfamiliar with the product and the proprietary name. The product unfamiliarity and any similarity in packaging among the Alcon otic and ophthalmic products reinforces the need to educate healthcare providers upon the Ciprodex launch in order to prevent errors.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

The Ciprodex labels and labeling were submitted in draft format, which did not allow for a comprehensive evaluation of the color, format, etc. However, DMETS has attempted to focus on safety issues relating to possible medication errors and identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

We recommend that the active ingredient be expressed in percent and mg/ml.

B. PATIENT INFORMATION INSTRUCTIONS

1. The statement prior to Instruction Four states: This
statement may be confusing to patients if they are unaware or unsure of their diagnosis.

2. Instruction Four

The picture should identify the location of the 'Tragus.'

3. Instruction Five

The picture should identify the location of the 'Outer Ear Lobe.'

2. Do Not Take By Mouth Section

The statement ~~_____~~ is confusing. What constitutes _____ ? Revise accordingly.

IV. **RECOMMENDATIONS:**

A. DMETS has no objection to the use of the proprietary name Ciprodex.

B.

In addition, to the labeling revisions outlined in Section III of this review, the Ciprodex labels and labeling should be clearly distinguished from other Alcon ophthalmic and otic products using contrasting design, color, boxing, or some other means.

C. DDMAC finds the proprietary name Ciprodex acceptable from a promotional perspective.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling 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 and established names from this date forward.

DMETS 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 Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Denise Toyer
4/9/03 03:39:15 PM
PHARMACIST

Carol Holquist
4/9/03 04:00:03 PM
PHARMACIST

Jerry Phillips
4/10/03 10:15:05 AM
DIRECTOR

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: April 7, 2003 **TIME:** 3:00 PM **LOCATION:** S-346

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex (ciprofloxacin/dexamethasone) Otic Suspension

BETWEEN:

Name:

David Stroman, PhD	Director, Anti-Infective Microbiology
Michael Pflieger, JD	Senior Director, Regulatory Affairs
Sheryl Dupre	Assistant Director, Clinical
Peter Conroy, PhD, JD	Associate Director, Clinical
Susan Potts, MS	Manager, Biostatistics
Darell Turner, PhD	Senior Director, Biostatistics
Michael Wall, PhD	Director, R&D Development
Seane Jones, MS, RAC	Assistant Director, Regulatory Affairs

Representing: Alcon Research Ltd.

AND

Name:

Jean Mulinde, MD	Medical Team Leader
Daphne Lin, PhD	Biostatistical Team Leader
Tom Smith, MD	Clinical Reviewer
Joel Jiang, PhD	Biostatistical Reviewer
LT Danny Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products (DAIDP), HFD-520

BACKGROUND:

On April 4, 2003 DAIDP sent Alcon a facsimile requesting that the sponsor conduct some additional biostatistical analyses on the data in the submission.

MEETING OBJECTIVE:

To clarify any questions the sponsor has regarding the request outlined in the Division's facsimile.

NDA # 21-537

PAGE #2

DISCUSSION AND RECOMMENDATIONS:

The sponsor agreed to provide the Division with the information requested in the facsimile (see attached fax).

Additionally, the following analysis will be added to #4 under AOE studies:

- Patients with any pathogens isolated at base line

ACTION ITEMS:

The presentation of the data from the additional analyses will be in the same format as the samples provided in the April 4, 2003 facsimile from DAIDP.

The sponsor will submit the additional biostatistical analyses by April 21, 2003.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Jean Mulinde, MD
Medical Team Leader

**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
Center for Drug Evaluation and
Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: April 4, 2003

To: Seane D. Jones, MS, RAC	From: LT Daniel Nguyen, RPh
Company: Alcon Research, Ltd.	Division of Anti-Infective Drug Products
Fax number: 817-551-4630	Fax number: 301-827-2325
Phone number: 817-568-6296	Phone number: 301-827-2125
Subject: Request for additional Ciprodex analyses.	

Total no. of pages including cover: 17

Comments: Please confirm the receipt of this fax with a follow-up email to me
(nguvenda@cder.fda.gov). Thank you.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Hi Seane,

This is a request for additional info/analyses from the Clinical and Biostatistical Reviewer. If you feel that a telecon is necessary for clarification on what they need, let me know ASAP via email.

Regards,
Danny

FAXED
4-4-03
10:30 AM

NDA # 21-537

Submission Date: September 25, 2002

Reviewer Comments

Page 1

Sponsor: Alcon Research, Ltd.

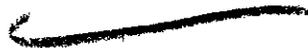
Product: Ciprodex Otic Suspension (ciprofloxacin 0.3% and dexamethasone 0.1%)

Request for additional Ciprodex analyses

1. Many of the microorganisms listed in the INDICATIONS AND USAGE section of the proposed label are not generally recognized pathogens in acute otitis externa (AOE) or acute otitis media in patients with tympanostomy tubes (AOMT). Please provide scientific justification for the inclusion of the following organisms:

AOE:





AOMT:

2. Provide revised per protocol (PP) and intent to treat (ITT) analyses for all studies. In these revised analyses, patients who were discontinued because of treatment failure should be included with the test of cure outcome assigned as failure.
3. For each proposed pathogen in the draft label, provide tables listing clinical and microbiologic outcomes at test of cure using the revised MPP and MITT populations for each study.

**APPEARS THIS WAY
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NDA # 21-537

Submission Date: September 25, 2002

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4. Using these revised PP and ITT populations, provide modified PP (MPP) and modified ITT (MITT) analyses for the following subsets of patients:

AOE studies:

- Patients with *Pseudomonas aeruginosa* or *Staphylococcus aureus*
- Patients with *P. aeruginosa*, *S. aureus*, or any other Gram-negative bacteria
- Patients with any organism in the proposed label

AOMT studies:

- Patients with *Streptococcus pneumoniae*, *S. aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *P. aeruginosa*
- Patients with any organism in the proposed label

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ON ORIGINAL

ANALYSES FOR CLINICAL RESPONSES AT TOC OF ITT AND PP SUBJECTS

For the four studies (98-18, 98-19, 99-59, and 00-52), please provide the analyses results for clinical responses at TOC of ITT and PP subjects, and the data files accordingly, after correcting and adjusting the evaluability status and outcome assessment for those discontinued from the study due to treatment failure.

TABLE 1: STUDY Cxx-xx: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 2: STUDY Cxx-xx: CLINICAL RESPONSES OF PP SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

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ON ORIGINAL**

**SUBGROUP ANALYSES FOR MICROBIOLOGICAL RESPONSES
AND CLINICAL RESPONSES AT TOC OF MITT AND MPP
SUBJECTS**

For AOE studies (98-18 and 98-19)

Note: For the MPP analysis, should also include those MITT subjects discontinued from the study due to treatment failure.

TABLE 3: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSE RATES BY PATHOGEN OF MITT SUBJECTS AT TOC		
Pathogen	Ciprodex	Comparator
Aerobic, Gram-Positive		
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
/	/	/
Aerobic, Gram-Negative		
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)
/	/	/

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 4: STUDY CXX-XX: MICROBIOLOGICAL RESPONSE RATES BY PATHOGEN OF MPP SUBJECTS AT TOC

Pathogen	Ciprodex	Comparator
<u>Aerobic, Gram-Positive</u>		
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
/	/	/
<u>Aerobic, Gram-Negative</u>		
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)
/	/	/

TABLE 5: STUDY CXX-XX: CLINICAL RESPONSE RATES BY PATHOGEN OF MITT SUBJECTS AT TOC

Pathogen	Ciprodex	Comparator
<u>Aerobic, Gram-Positive</u>		
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
/	/	/
<u>Aerobic, Gram-Negative</u>		
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)
/	/	/

TABLE 6: STUDY CXX-XX: CLINICAL RESPONSE RATES BY PATHOGEN OF MPP SUBJECTS AT TOC		
Pathogen	Ciprodex	Comparator
<u>Aerobic, Gram-Positive</u>		
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
<u>Aerobic, Gram-Negative</u>		
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)

Set One:

Including subjects with any pathogens isolated at baseline:

(1) MICROBIOLOGICAL RESPONSES

TABLE 7: STUDY CXX-XX: MICROBIOLOGICAL RESPONSES OF MITT SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 8: STUDY CXX-XX: MICROBIOLOGICAL RESPONSES OF MPP SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

NDA # 21-537

Submission Date: September 25, 2002

Reviewer Comments

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(2) CLINICAL RESPONSES

TABLE 9: STUDY C_{XX-XX}: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 10: STUDY C_{XX-XX}: CLINICAL RESPONSES OF MPP SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

**APPEARS THIS WAY
ON ORIGINAL**

Set Two:

Including subjects with the following pathogens or pathogen classes isolated at baseline:

Pseudomonas aeruginosa

Staphylococcus aureus

And excluding those with:

(1) MICROBIOLOGICAL RESPONSES

TABLE 11: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MITT SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 12: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MPP SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

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(2) CLINICAL RESPONSES

TABLE 13: STUDY C_{xx-xx}: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 14: STUDY C_{xx-xx}: CLINICAL RESPONSES OF MPP SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

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ON ORIGINAL**

NDA # 21-537

Submission Date: September 25, 2002

Reviewer Comments

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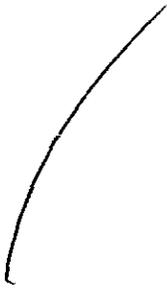
Set Three:

Including subjects with the following pathogens or pathogen classes isolated at baseline:

Pseudomonas aeruginosa

Staphylococcus aureus

And excluding those with:



(1) MICROBIOLOGICAL RESPONSES

TABLE 15: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MITT SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 16: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MPP SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

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Submission Date: September 25, 2002

Reviewer Comments

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(2) CLINICAL RESPONSES

TABLE 17: STUDY Cxx-xx: CLINICAL RESPONSES OF MIT SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 18: STUDY Cxx-xx: CLINICAL RESPONSES OF MPP SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

**APPEARS THIS WAY
ON ORIGINAL**

For AOMT studies (99-59 and 00-52)

Note: For the MPP analysis, should also include those MITT subjects discontinued from the study due to treatment failure.

TABLE 19: STUDY C_{xx-xx}: MICROBIOLOGICAL RESPONSE RATES BY PATHOGEN OF MITT SUBJECTS AT TOC

Pathogen	Ciprodex	Comparator
Aerobic, Gram-Positive		
<i>Streptococcus pneumoniae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
Aerobic, Gram-Negative		
<i>Haemophilus influenzae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Moraxella catarrhalis</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)

TABLE 20: STUDY C_{xx-xx}: MICROBIOLOGICAL RESPONSE RATES BY PATHOGEN OF MPP SUBJECTS AT TOC

Pathogen	Ciprodex	Comparator
Aerobic, Gram-Positive		
<i>Streptococcus pneumoniae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
Aerobic, Gram-Negative		
<i>Haemophilus influenzae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Moraxella catarrhalis</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)

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TABLE 21: STUDY Cxx-xx: CLINICAL RESPONSE RATES BY PATHOGEN OF MITT SUBJECTS AT TOC		
Pathogen	Ciprodex	Comparator
Aerobic, Gram-Positive		
<i>Streptococcus pneumoniae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
Aerobic, Gram-Negative		
<i>Haemophilus influenzae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Moraxella catarrhalis</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)

TABLE 22: STUDY Cxx-xx: CLINICAL RESPONSE RATES BY PATHOGEN OF MPP SUBJECTS AT TOC		
Pathogen	Ciprodex	Comparator
Aerobic, Gram-Positive		
<i>Streptococcus pneumoniae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Staphylococcus aureus</i>	9/10 (90.0%)	9/10 (90.0%)
Aerobic, Gram-Negative		
<i>Haemophilus influenzae</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Moraxella catarrhalis</i>	9/10 (90.0%)	9/10 (90.0%)
<i>Pseudomonas aeruginosa</i>	9/10 (90.0%)	9/10 (90.0%)

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NDA # 21-537

Submission Date: September 25, 2002

Reviewer Comments

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Set One:

Including subjects with any pathogens isolated at baseline:

(1) MICROBIOLOGICAL RESPONSES

TABLE 23: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MITT SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 24: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MPP SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

(2) CLINICAL RESPONSES

TABLE 25: STUDY Cxx-xx: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 26: STUDY Cxx-xx: CLINICAL RESPONSES OF MPP SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

Set Two:

Including subjects with the following pathogens or pathogen classes isolated at baseline:

- *Streptococcus pneumoniae*
- Staphylococcus aureus*
- Haemophilus influenzae*
- Moraxella catarrhalis*
- Pseudomonas aeruginosa*

(1) MICROBIOLOGICAL RESPONSES

TABLE 27: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MITT SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

TABLE 28: STUDY Cxx-xx: MICROBIOLOGICAL RESPONSES OF MPP SUBJECTS AT TOC		
Microbiological Response	Ciprodex	Comparator
Success	102 (100%)	100 (100%)
Not Success	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

(2) CLINICAL RESPONSES

TABLE 29: STUDY Cxx-xx: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC		
Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

NDA # 21-537

Submission Date: September, 25, 2002

Reviewer Comments

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Clinical Response	Ciprodex	Comparator
Cure	102 (100%)	100 (100%)
Not Cure	22 (78.1%)	20 (72.8%)
Difference in Response Rate Ciprodex vs. Comparator:	2.2%, 95% C.I.: -3.0%, 5.5%	

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

/s/

Daniel Nguyen
4/4/03 10:39:27 AM
CSO
fax comments clin & stat 04-04-03
Please sing off

Frances LeSane
4/10/03 09:39:53 AM
CSO

Jean Mulinde
4/11/03 09:37:35 AM
MEDICAL OFFICER

APPEARS THIS WAY
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ORIG AMENDMENT

N-000/BP

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March 28, 2003

ALBION
RESEARCH, LLC.

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

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Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

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MAR 31 2003

MEGA/CDER

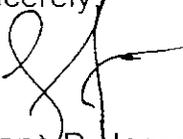
**RE: NDA 21-537, CIPRODEX™ OTIC SUSPENSION
Amendment – PK Technical Report 003:69:0303**

Dear Sir/Madam:

Enclosed is the PK Technical Report 003:69:0303 analyzing 10 patients combined from clinical PK studies C-00-68 and C-02-58. The Technical Report and its contents were agreed upon by the Agency in our February 5, 2003 teleconference.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

ORIGINAL

7 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Airborne Express Airbill Number 4340371066

March 18, 2003

COPY

Alcon
RESEARCH, Ltd.

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

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Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

RE: IND 54,670
CIPRODEX™ OTIC SUSPENSION
IND Amendment – Amendment to C-02-58
SN: 045

Dear Sir/Madam:

Alcon Inc., hereby submits a protocol amendment in accordance with 21 CFR 312.30(b).

Please be advised that IND 54,670 is being amended to add an interim lock of the database as discussed with the Agency, clarify the plasma collection and processing, allow 2 short-acting antibiotics and add 2 additional investigators.

Enclosed in triplicate is the protocol amendment detailing the above mentioned changes.

The above referenced IND is being amended with two additional US physicians as principal investigators for the C-02-58 Clinical PK protocol. Enclosed for each of these investigators are their respective 1572 forms, CV's and IRB information.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,


Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

TELECON MINUTES

Meeting Date: February 5, 2003 **Time:** 2:30-3:00 P.M.
Location: Corporate Building **Sponsor:** Alcon research, Ltd.
NDA Number: 21-537, Ciprodex[®] Otic Suspension
IND Number: 54,670, Ciprodex[™] Otic Suspension

Participants from Division of Anti-Infective, HFD-520:

Janice Soreth, M.D., Division Director
Phil Colangelo, Ph.D., Team Leader, Bio-Pharmaceutics
Paul Buehler, Ph.D., Reviewer, Bio-Pharmaceutics
Thomas Smith, M.D., Clinical Reviewer
Frances V. LeSane, Chief, Project Management Staff
Daniel Nguyen, Pharm. D., Project Manager
Susmita Samanta, M.D., Project Manager

Participants from Alcon:

Seane Jones	Regulatory Affairs
Michael Wall	Otic/Nasal Product Development
Peter Conroy	Clinical Sciences
Darell Turner	Biostatistics
Ken Sullivan	Biostatistics
Susan Potts	Biostatistics
Lewis Silver	Product Safety
David Dahlin	Pharmacokinetics
Robert Faulkner	Pharmacokinetics
Mark Jasek	Pharmacokinetics

Background:

On September 23, 2002, Alcon submitted a New Drug application for Ciprodex[®] Otic Suspension. Part of this NDA was a PK study, number C-00-68, conducted in two centers, one in _____, one in _____. Because of protocol violation reported in the _____ center, the Division could not accept the data generated in that center. On January 16, 2003, Alcon submitted a new Phase I protocol, C-02-58, to obtain additional patients to meet the required number of patients for this PK study. This teleconference was scheduled to discuss the timeline for the current study C-02-58.

After introduction of the attendees, the following discussion took place:

- The Division notified Alcon that the Final Study Report (FSR) for C-02-58 should be submitted to the NDA before April 25, 2003, which is ninety days before the action date of this NDA. This ensures enough time to review the new data and incorporate the information in the labeling.

- The FSR should contain the safety analysis, validation of methods, assessment of adverse reactions.
- The Sponsor explained that they are trying to obtain six more patients in this study and expect to complete it before April 25, 2003. The Sponsor agreed to provide the FSR before this date
- The Sponsor also agreed to provide electronic and paper copies of the data and the tables.

Minutes prepared by: Susmita Samanta
Concurred by: Janice Soreth, M.D.

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

/s/

Janice Soreth
3/4/03 01:35:45 PM

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January 21, 2003

Alcon
RESEARCH, Ltd.

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

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(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

RE: CIPRODEX™ OTIC SUSPENSION, NDA 21-537
Four Month Safety Update

Dear Sir/Madam:

Alcon, Inc. hereby submits three copies of the four-month safety update for Ciprodex Otic Suspension per CFR 314.50 and 505(i) of the act.

Since the filing of the Ciprodex Otic Suspension on September 23, 2002 no additional clinical trials have been initiated with Ciprodex Otic Suspension during the subsequent four-month period. In addition, there were no ongoing clinical studies at the time of the NDA submission. Thus, there is no new clinical safety data to report in this four-month post-NDA safety update.

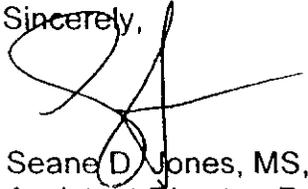
However post-submission review of the NDA revealed that a safety statement was made in the precaution section of the package insert (Module 1, 3.B.1) for which no supportive study was included;

"No signs of local irritation were found when CIPRODEX® Otic was applied topically in the rabbit eye."

and for this reason, an initial oversight was made in failing to include the technical report to support the safety statement made in the submitted package insert. Enclosed please find the attached technical report 099:30:0202 (belongs in Module 4, 4.2.3.2) and Toxicology Tabulated Summary Table 2.6 7.3 E (Module 2, 2.6.7.3.E) for consideration and support of this statement. We apologize for this oversight.

If there are any questions or comments concerning this information, please contact me at 817/ 568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

cc: Lt. Daniel Nguyen, Project Manager Division of Anti-Infective Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

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November 18, 2002

Alcon
RESEARCH, LTD.

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

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Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

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NOV 19 2002

MEGA/CDER

82
ORIG AMENDMENT

RE: **NDA 21-537**
CIPRODEX® OTIC SUSPENSION
Case Report Forms For: C-99-59, C-00-52, C-98-19 and C-98-18;
Import SAS Transport Files Program and Microbiologist Answer to Question

Dear Sir/Madam:

As per the November 6, 2002 teleconference between FDA and Alcon we are providing CD copies of the Case Report Forms from clinical studies: C-99-59, C-00-52, C-98-19 and C-98-18, as requested.

Also provided in this submission is the import SAS transport files program to aid the reviewing statisticians.

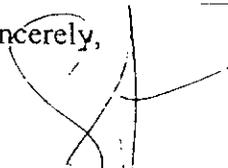
Following the teleconference Dr. Harold Silver, reviewing microbiologist, requested the location of the semi-quantitative data. An email response to this question was given on November 12, 2002. Attached is that email response.

This should complete the action items owed to the Agency to complete your fileability review of our NDA 21-537.

Should you need additional copies we will be glad to accommodate.

If there are any questions or comments concerning this submission, please contact me by telephone at 817/568-6296 or via facsimile at 817/551-4630.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

ORIGINAL

Airborne Express Airbill Number 4340369865

Alcon
RESEARCH, Ltd.

October 31, 2002

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Lt. Danny Nguyen
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

Sm
ORIG AMENDMENT

RECEIVED

NOV 01 2002

MEGACODER

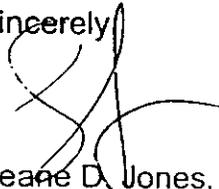
RE: **NDA 21-537**
CIPRODEX® OTIC SUSPENSION
Clinical Treatment Code Tables, Complete Data Sets With Patient
ID's & Patient Codes And Reasons For Exclusion Codes

Dear Lt. Nguyen:

As per our teleconference this afternoon we are providing the clinical treatment code tables, complete data sets with patient IDs and patient codes and reasons for exclusion codes.

If there are any questions or comments concerning this submission, please contact me directly at 817/568-6296.

Sincerely,


Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as Indicated.

Airborne Express Airbill Number 1113247461

October 2, 2002

NEW CORRESPONDENCE
NC

RECEIVED

Dr. Susmita Samanta and
Dr. Danny Nguyen
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway,
Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones: M.S., R.A.C.
Assistant Director
Regulatory Affairs

RECEIVED

OCT 03 2002

MEGA/CDER

**RE: NDA 21-537, CIPRODEX® OTIC SUSPENSION
SAS Transport Files (CDs) and Electronic Review Aide CDs**

Dear Drs. Samanta and Nguyen:

I am enclosing 2 copies of the SAS transport files (CDs) as promised.

Also included in this mailing are 5 copies of the electronic review aide for our NDA submission. Our publishing group has printed 5 copies of instructions of how to access these CDs, for ease of use.

If you need additional copies we will be glad to accommodate your requests.

If there are any questions or comments concerning this information, please contact me at 817/568-6296.

Sincerely,



Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs

Enclosures as indicated.

ORIGINAL

September 23, 2002

COPY**Alcon**
LABORATORIES, Ltd.

Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Seane D. Jones, M.S., R.A.C.
Assistant Director
Regulatory Affairs

RE: NDA 21-537
CIPRODEX[®] OTIC SUSPENSION
(ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension)
Original New Drug Application – User Fee ID #4412
EXPEDITED REVIEW REQUESTED

Dear Sir/Madam:

As an authorized U.S. representative of Alcon, Inc., I hereby submit an original New Drug Application (NDA) for Ciprodex[®] Otic Suspension. This NDA is being submitted pursuant to 21 CFR §314.54 and Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The drug product will be marketed as a prescription product and is indicated for the topical treatment of otic bacterial infections and inflammation (AOMT and AOE).

Alcon requests an expedited review of our NDA application, CIPRODEX Otic Suspension. Our basis for requesting an expedited review is detailed in an attachment immediately following this cover letter.

Ciprofloxacin hydrochloride as well as the trademark name CIPRODEX[®] is licensed from Bayer AG, who manufactures Cipro[®] for the treatment of various infections. A letter of authorization from Bayer AG granting permission to reference their U.S. DMF is included in Module 3 (3.2.S).

This application was prepared in the common technical document format in accordance with FDA and ICH guidance documents.

This application consists of an archival copy and review copy. These copies have been generated utilizing CoreDossier.

Consistent with the FDA guidance, Submitting Marketing Applications According to the ICH-CTD Format – General Considerations, pagination is at the document

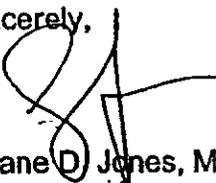
NDA 21-537
CIPRODEX® OTIC SUSPENSION
Page 2
September 23, 2002

level, volumes are identified by module and numbered sequentially within a module.

A list of the facilities listed in this application is included as an attachment in Module 1. All the facilities listed are ready for inspection.

If there are any questions or comments concerning this submission, please contact me by telephone at 817/568-6296 or via facsimile at 817/551-4630.

Sincerely,



Seane D Jones, MS, RAC
Assistant Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

TELECOM MEETING MINUTES

MEETING DATE: 11-8-02

TIME: 11:00 am

LOCATION: S-346

DRUG: Ciprodex Otic Suspension

APPLICATION #: 21537

SPONSOR: Alcon

FDA ATTENDEES:

<u>NAME</u>	<u>TITLE</u>
Daphne Lin	Biostatistics Team Leader
Joel Jiang	Biostatistics
Danny Nguyen	Project Manager

EXTERNAL ATTENDEES:

<u>NAME</u>	<u>TITLE</u>
Darrell Turner	Biostatistics
Susan Potts	Biostatistics
Gary Elliott	Biostatistics
Michael Pflieger	Regulatory Affairs

MEETING OBJECTIVES:

- To clarify additional data set issues discovered by the FDA.

DISCUSSION AND RECOMMENDATIONS:

- FDA conveyed to the sponsor the discrepancy that FDA discovered in the data sets between the SAS transport files data sets and the raw data sets (version 8) submitted as desk copy to the FDA. There are more data sets in the raw data sets (version 8) for certain studies when compared to the number of data sets originally submitted as SAS transport files for the same studies.
- The sponsor conveyed to the FDA the extra data sets present in the raw data sets (version 8) are used to calculate confidence intervals only.
- To avoid further confusions with the data sets, the sponsor suggested that they will submit to the FDA, as desk copy, the software used to convert SAS transport files data sets (version 6) to raw data sets (version 8). FDA concurs.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

There are no unresolved issues.

ACTION ITEMS:

- None.

LT Daniel K. Nguyen
Regulatory Health Project Manager

Jean Mulinde, M.D.
Medical Team Leader

Drafted by: DKN 11-18-02
Initiated by: SS
Final: date

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ON ORIGINAL**

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/s/

Daniel Nguyen
1/6/03 12:20:56 PM
CSO
11-8-02 Telecon Minutes
Please sign off

Daphne Lin
1/6/03 04:05:01 PM
BIOMETRICS

Joel Jiang
1/9/03 10:55:36 AM
BIOMETRICS

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: November 6, 2002 **TIME:** 3:00 PM **LOCATION:** S-346

APPLICATION NUMBER: NDA 21-537

DRUG NAME: Ciprodex Otic Suspension (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension)

BETWEEN:

Name:

Michael Wall, PhD	Director, Otic/Nasal Product Development
Michael Pflieger, JD	Sr. Director, Consumer Products, Otic/Nasal Prod., Regulatory Affairs
Seane Jones, MS, RAC	Assistant Director, Otic/Nasal Products, Regulatory Affairs
Darell Turner, PhD	Sr. Director, Biostatistics & Clinical Data Management
Susan Potts, MS	Manager, Biostatistics, ENT & Anti-Infectives, Biostatistics & Clinical Data Management
Gary Elliott, MS	Manager, SAS Programming, Biostatistics & Clinical Data Management
David W. Stroman, PhD	Director, Anti-Infective Microbiology
Peter J. Conroy, PhD, JD	Associate Director, Clinical Science, Otic/Nasal Product Development
Leslie E. Lemke, MS, PhD	Sr. Scientist, Otic/Nasal, Toxicology
David Dahlin, PhD	Senior Director, PK/ADME, Pharmacokinetics/Drug Metabolism
Gail Hogg, BS	Senior Product Safety Specialist II
Robert Faulkner, PhD	Director, Clinical Pharmacology, Pharmacokinetics
James E. Chastain, PhD	Assistant Director, Pharmacokinetics/Drug Metabolism, Pharmacokinetics
Sheryl Dupre, BS	Assistant Director, Otic Clinical Development
Lewis H. Silver, PhD	Senior Director, Product Safety

Representing: Alcon Research, Ltd.

AND

Name:

Janice Soreth, MD	Director
Jean Mulinde, MD	Medical Team Leader
Tom Smith, MD	Clinical Reviewer
Daphne Lin, PhD	Biostatistics Team Leader
Joel Jiang, PhD	Biostatistics Reviewer
Phil Colangelo, PharmD, PhD	Biopharmaceutics Team Leader
Sue Chih Lee, PhD	Biopharmaceutics Reviewer
Susmita Samanta, MD	Regulatory Health Project Manager
LT Daniel Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products, HFD-520

MEETING OBJECTIVES:

1. The need for additional Case Report Forms.
2. Discuss status of the PK study (investigation into the protocol violation with study # C-00-68 Clinical PK Study at _____)
3. Discuss the reasons why the FDA is not granting Alcon's request for expedited review of the NDA.

DISCUSSION AND RECOMMENDATIONS:

1. The Division requested that the sponsor submit additional Case Report Forms in PDF format. The Division agreed to fax a list of patient numbers, categorized by study, by COB 11-07-02.
2. The Division anticipates that the Division of Scientific Investigation (DSI) will find the PK data from Dr. _____ to be unacceptable due to issues with data integrity. Therefore, the Division recommends that the sponsor select another clinical site and repeat the PK study. The sponsor asked the Division if the PK data from the four existing patients at the _____ clinical site would be enough to support the NDA provided the sponsor agreed to perform a separate PK study as a Phase IV Commitment. The Division stated that the data from the four patients at the _____ clinical site are not acceptable alone and that another PK study would be necessary. The sponsor agreed to conduct another PK study identical to the one already conducted. The Division will accept study results from ten new patients plus the four _____ patients to support the PK for Ciprodex.
3. The sponsor will submit the PK study protocol to the Division within the next two to three weeks.
4. The Division stated that expedited review was not granted for the NDA because:
 - a. The proposed indication is not considered serious or life threatening.
 - b. There are multiple alternatives for the treatment of the disease state.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

Jean Mulinde, MD
Medical Team Leader

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this page is the manifestation of the electronic signature.**

/s/

Daniel Nguyen

3/13/03 01:30:05 PM

CSO

11-06-02 Telecon Minutes. Draft: MDP, SS, JJ, DL, TS,

JM, PC, JS

Please sign off

Frances LeSane

3/13/03 05:57:25 PM

CSO

Jean Mulinde

3/14/03 07:53:19 AM

MEDICAL OFFICER

Janice Soreth

3/17/03 04:44:44 PM

MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2002

To: Seane D. Jones	From: LT Daniel Nguyen
Company: Alcon Research LTD	Division of Division of Anti-Infective Drug Products
Fax number: 817-551-4630	Fax number: 301-827-2325
Phone number: 817-568-6296	Phone number: 301-827-2125

Subject: Stat and Clinical comments on SAS data sets

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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FAXED
 11-4-02
 4pm

FAXED
 11-5-02
 10:15A

2nd fax,
 sponsor never verified
 the 1st.
 Verified receipted
 C. Lumberton

Statistical Comments
NDA 21,537 (Ciprodex)

General Rules for Submission of Data Sets Requested by Statistical Reviewer:

1. Each subject must be identified with a single, unique number for the entire application.
2. The variables should be represented as column headings with each result or observation for an individual subject in the rows, allowing for multiple rows per subjects.
3. When at all possible, the same variable names and codes should be used across studies.
4. Include variable descriptions and codes in the column header.
5. The format of variables for similar types of data should also be consistent within and across studies.
6. Data variable names should be limited to 8 characters with a more descriptive name, up to 32 characters, provided as data variable label.

According to the Guidance for Industry: Providing Regulatory Submissions to Office of Food Additive Safety in Electronic Format-General Considerations, each data set as a SAS transport file should be provided.

The major problems encountered with the data files submitted are:

1. The values or codes of some variables seem unidentified and not interpretable (See attached examples). [If the regular SAS data sets are adequately set as assumed, the problems for those codes and values that are not interpretable or unidentified might have been caused when sequential file formats (transport files) were created. The Sponsor will need to review all SAS transport files submitted in support of the NDA to resolve these issues.]
2. There is only one SAS "format.sc2" for the data sets of Study C0052, but none for the other studies.

Clinical Comment

Can the Applicant identify the location in the Electronic Review Aid where a listing of the code definitions used in each data set (similar to those provided for the evaluability data set in the October 31, 2002 submission) can be found. If such a listing is not available, please provide as an amendment to the NDA.

FAXED
11-4-02

4pm

FAXED
11-5-02

10:15A

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/s/ [redacted]

Daniel Nguyen
11/4/02 03:12:22 PM
CSO

Faxed on 11/4/02

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ON ORIGINAL**

MODE = MEMORY TRANSMISSION

START=NOV-04 16:00

END=NOV-04 16:22

FILE NO. = 058

STATION NO.	COM	ABBR NO.	STATION NAME/TEL. NO.	PAGES	DURATION
201	634	a	98175514630	022/004	00:00:00

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***** -FDA-CDER-DAIDP - ***** 321 827 2325- *****



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2002

To: Seane D. Jones	From: LT Daniel Nguyen
Company: Alcon Research LTD	Division of Division of Anti-Infective Drug Products
Fax number: 817-551-4630	Fax number: 301-827-2325
Phone number: 817-568-6296	Phone number: 301-827-2125
Subject: Stat and Clinical comments on SAS data sets	

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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Division of Anti-Infective Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-520
Rockville, MD 20850

FAXED (Received)
11-7-02
11:20A

facsimile transmittal

original based on
11-6-02 4:14 pm
(top got cut off)

To: *Michael Pfloger*

Fax: 817-551-4630

From:



LT Daniel K. Nguyen
Regulatory Health Project Manager
FDA / Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products
Phone: (301) 827-2125 Fax: (301) 827-2324

Date:

11-7-02

Re: *ReFax list of pt. #'s*

Pages: 16

CC:

Urgent

For Review

Please Comment

Please Reply

Please Recycle

Notes: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

TELECOM MEETING MINUTES

MEETING DATE: 10-31-02

TIME: 4:00 pm

LOCATION: S-346

DRUG: Ciprodex Otic Suspension

APPLICATION #: 21537

SPONSOR: Alcon

FDA ATTENDEES:

NAME

Jean Mulinde

Tom Smith

Daphne Lin

Joel Jiang

Susmita Samanta

Danny Nguyen

TITLE

Medical Team Leader

Medical Officer

Biostatistics Team Leader

Biostatistics

Project Manager

Project Manager

EXTERNAL ATTENDEES:

NAME

Darrell Turner

Susan Potts

Gary Elliott

Michael Wall

Michael Pflieger

Seane Jones

TITLE

Biostatistics

Biostatistics

Biostatistics

Project Manager

Regulatory Affairs

Regulatory Affairs

MEETING OBJECTIVES:

- To clarify issues that Dr. Jiang (Biostatistics) has concerning the SAS transport files data sets that were submitted by the sponsor.

DISCUSSION AND RECOMMENDATIONS:

- FDA conveyed to sponsor that there might be some technical problem with the SAS transport files data sets that were submitted.
 1. When data sets from the SAS transport files were extrapolated into JMP4, unidentifiable variables appear.
 2. There are no definition sets for the variables.
- Sponsor agree to overnight to FDA (as desk copies):
 1. Data sets with patient # and treatment code for each of the four pivotal studies on SAS transport files in CDs (three copies).
 2. Hard copy set of definitions for the variables.
- FDA recommended for the sponsor to look into the possibility of problems in converting the raw SAS data sets into SAS transport files.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- FDA will follow up with the sponsor on their analysis of possible technical problems with the SAS transport files data sets that was submitted.
- Sponsor emailed to FDA their rationale for expedited review of Ciprodex Otic Suspension (attached) requesting the explanation for FDA decline for expedited review.

ACTION ITEMS:

- None.

LT Daniel K. Nguyen
Regulatory Health Project Manager

Jean Mulinde, M.D.
Medical Team Leader

Drafted by: DKN / 11-18-02
Initialed by: SS
Final: date

**APPEARS THIS WAY
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/s/

Daniel Nguyen
1/6/03 12:31:18 PM
CSO
10-31-02 Telecon Minutes
Please sign off

Daphne Lin
1/6/03 04:06:19 PM
BIOMETRICS

Jean Mulinde
1/8/03 07:05:03 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-537

Alcon Research, Ltd.
Attention: Seane D. Jones, MS, RAC
Assistant Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Jones:

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: CIPRODEX® OTIC SUSPENSION, (Ciprofloxacin HCL
0.3%/Dexamethasone 0.1% otic suspension)

Review Priority Classification: Standard (S)

Date of Application: September 23, 2002

Date of Receipt: September 25, 2002

Our Reference Number: NDA 21-537

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 25, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857

NDA 21-537

Page 2

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Anti-Infective Drug Products, HFD-520

Attention: Document Room

9201 Corporate Blvd.

Rockville, MD 20850

If you have any questions, call LT Daniel Nguyen, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane

Chief, Project Management Staff

Division of Anti-Infective Drug Products, HFD-520

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

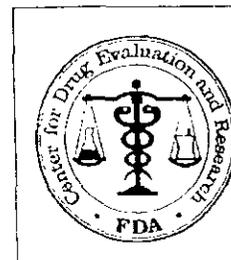
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/s/

Frances LeSane
10/11/02 04:17:27 PM

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ON ORIGINAL**

INDUSTRY MEETING MINUTES



Meeting Date: February 13, 2002

Location: Corporate Building --Room S-300

IND: 54,670

Drug: CiproDex™™ Otic Suspension
(0.3% ciprofloxacin hydrochloride and 0.1% dexamethasone)

Sponsor: Alcon Research, Ltd.

Type of Meeting: Pre-NDA

Meeting Chair: Dikoe Makhene, M.D.
Clinical Team Leader
Division of Anti-infective Drug Products (HFD-520)

Minutes Recorder: Susmita Samanta/ Project Manager

FDA Attendees:

Janice Soreth, M.D.
Dikoe Makhene, M.D.
Tom Smith, M.D.
David Roeder
Jenny Zheng, Ph.D.
Frank Pelsor, Ph.D.
Albert Sheldon, Ph.D.
Daphne Lin, Ph.D.
Joel Jiang, Ph.D.
Harold Silver
David Katague, Ph.D.
Milton Sloan, Ph.D.
Terry Peters, D.V.M.
Amy Ellis, Ph.D.
Susmita Samanta

Titles:

Division Director
Medical Team Leader
Clinical Reviewer
Associate Director for Regulatory Affairs
Clinical Pharmacology Reviewer
Team Leader/Clinical Pharmacology
Team Leader/Microbiology
Team Leader/Statistics
Statistical Reviewer
Microbiology Reviewer
Chemistry Team Leader
Chemistry Reviewer
Acting Pharmacology Team Leader
Pharmacology Reviewer
Project Manager

Offices:

HFD-520
HFD-520
HFD-520
HFD-104
HFD-520
HFD-520
HFD-520
HFD-725
HFD-725
HFD-520
HFD-520
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HFD-520

Alcon Research Attendees:

Dr. Michael Wall
Mr. Michael Pflieger
Ms. Seane Jones
Dr. Leslie Lemke
Dr. Peter Conroy

Titles:

ENT Products R&D
Regulatory Affairs
Regulatory affairs
Toxicology

Dr. Peter Roland	Clinical
Dr. Perrin White	Medical Advisor
Dr. Robert Faulkner	Medical Advisor
Dr. David Stroman	Clinical Pharmacology
Ms. Susan Potts	Microbiology
Dr. Joe Bullock	Biostatistics
Dr. Kent Sternitzke	Pharmaceutics
	Analytical Chemistry

Background Information:

The Sponsor plans to submit an NDA in second quarter of 2002 to provide for the use of CiproDex™ Otic Suspension in the treatment of acute otitis externa and acute otitis media with tympanostomy tubes. The Sponsor requested a pre-NDA meeting with the Division on December 21, 2001 to discuss various questions. The briefing document was received on December 26, 2001.

Discussion Points:

After introduction of the meeting attendees, the following questions were discussed.

Chemistry:

1. Does the FDA agree that the drug product tests and specifications are acceptable (see Tables 2.2-3 and 2.2-8)?

The tests appear to be acceptable. The specifications of the total degradants for each active seem loose and are without justification. Recommend re-examination of the specifications for degradants with a view toward tightening.

2. We propose to submit in the NDA — drug product stability data in support of an — expiry date for the drug product. Is this acceptable to the FDA?

Yes, in addition — of accelerated data should be included. A statistical analysis of the data showing projected shelf-life should also be included. The Sponsor has agreed to look at — data.

Toxicology:

3. Alcon proposes to submit all preclinical toxicology reports for the two active ingredients in CiproDex™ otic suspension with the NDA in early summer 2002. The final toxicology study conducted to determine the safety of CiproDex™ degradation products in the guinea pig middle ear will not be available until August 2002. Is it

acceptable to file the NDA with the in-life phase of this study to be followed by the final complete report in August 2002?

Normally, we would not be averse to accepting a final report of one study after the NDA has been filed (especially one focusing on degradation products in the suspension that is not really expected to demonstrate any ototoxicity). However, the Division sought assurance that the sponsor will submit the report in a timely manner during the NDA review period. Review of the report will be needed for the Division to take a final action. The Sponsor agreed.

4. The safety of Ciprofloxacin and Dexamethasone is well known. These agents are in many marketed products with indications for administration by intravenous, oral and topical routes. Due to the well characterized nature of these active ingredients, Alcon Corporate Toxicology plans to support the preclinical Toxicology of ciprofloxacin and dexamethasone in the NDA submission by referencing the published literature data and Alcon ototoxicity data presented in this briefing packet. Does the agency have comments in regards to this plan?

Use of data from the published scientific literature on ciprofloxacin and dexamethasone systemic toxicities to support the CiproDex™ NDA is acceptable, but it would also be helpful to get permission to cross reference the NDA for oral or IV Cipro. Data from the Cipro NDAs would be used to write some sections of the proposed label (Mutagenesis/Carcinogenesis and Pregnancy/Reproduction sections) for this product; the labels for all Cipro products (including the Cipro HC Otic Suspension) should be consistent.

Nonclinical PK:

5. Does the FDA agree that Alcon can support the preclinical pharmacokinetics and disposition of ciprofloxacin and dexamethasone by referencing data reported in the literature and data generated by BAYER AG?

The Sponsor's plan to use data from the literature and to cross reference Bayer's data is acceptable to the Division.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical PK:

6. Does the FDA agree that study C-00-68 is adequate to provide systemic safety pharmacokinetic data of ciprofloxacin and dexamethasone in children for the AOE and AOMT indications?

The division agrees and recommends inclusion of exposure (AUC) in the analysis of the results of study C-00-68 for the NDA. Also, the Sponsor should reconcile the doses (mL/drop) of ciprofloxacin and dexamethasone administered in the study C-00-68 with the dose (mL/drop) recommended in the final product label.

7. Does the FDA agree that because of the low plasma concentration and short duration of treatment, no specific evaluation of the effects on HPA axis suppression is necessary for CIPRODEX™ administered by the topical otic route?

The Sponsor will submit the literature referred to in the briefing document first for Divisional review.

Clinical:

8. Does the Agency agree that Alcon's justification for (a) concentration of 0.3% ciprofloxacin and 0.1% dexamethasone; and (b) posology (4 drops, twice daily for 7 days) is acceptable?

If these are the dose and regimen used in the studies, they are acceptable. (This was confirmed by the Sponsor).

9. Is Alcon's plan to file an NDA for an AOMT indication in pediatric patients based on the results from two studies demonstrating that CiproDex™ Otic Suspension is superior to CILOXAN Solution (C-99-59) and non-inferior to FLOXIN Otic Solution (C-00-52) acceptable?

The Division does not have any specific issue regarding this plan. The clearest win is when the study drug shows superiority but without that it is important to show that use of CiproDex™ provides an advantage to use of ciprofloxacin alone.

10. Given the demonstration of the effect of the steroid component (dexamethasone) in the time to end of otorrhea for the AOMT indication, is Alcon's plan to file an AOE indication acceptable?

This is a review issue. As mentioned before, data needs to show use of CiproDex™ provides clear advantage of the combination over plain ciprofloxacin.

Comments from Statistical reviewer:

- The Sponsor should clarify the definition of the primary efficacy variable. The briefing package contains inconsistency in this regard. In the protocol, the definition

of primary efficacy variable is clinical improvement as measured on a 4-point scale at the TOC visit which means that patients declared as cured and improved should be included as success. However, the tables displaying the results included only those patients with clinical cure as success and excluded patients classified as clinical improvement.

Microbiology:

11. Although _____ is considered normal skin flora, it is also recognized as a pathogen in ocular infections, endocarditis, intravenous catheter infections, bacteremia, osteomyelitis, wound infections, and urinary tract infections. Does the FDA agree that, if evidence is presented on specific strains and their association with otic infections (i.e., AE, AOMT) as distinct from the strains recovered from healthy ear canals and a sufficient number of successful outcomes are achieved _____ can be listed in the package insert as one of the species for which CiproDex™ is indicated.

The Sponsor will need to show clinical efficacy and indication relevancy and provide justification for addition of any organisms to the list of pathogens, other than recognized pathogens of AOMT or AE. Only those pathogens allowed in the Indication and Usage section will be allowed in the label. The ciprofloxacin HC otic suspension and ofloxacin otic solution labels are examples the Sponsor can refer to.

Additional Comments:

- The package insert will only contain a first list because the second list is based on breakpoints which reflect drug concentrations in blood. Since breakpoints are not established for topical drug products, the second list is not appropriate.
- As to the data to be analyzed, the Sponsor should use M-23 of the NCCLS, since breakpoints are not established for topical drugs, some sections may not be relevant.
- The Sponsor was provided with the desired Table of Contents (TOC) for "Item 7. Microbiology Section of a New Drug Application". The Sponsor was asked to submit the NDA with topics and headings as described in the "Table of contents" (TOC).
- The Sponsor was asked if they had performed any "semi-quantitative culture technique" procedures to help characterize the presence of pathogens in microbiological samples. They stated that they did and agreed to provide information on the semi-quantitative technique used and the results obtained.

Regulatory:

12. Alcon intends to submit an NDA for CiproDex™ Otic in 2002 utilizing the CTD format. Is this acceptable?

It is acceptable. The Division will work with the Sponsor since it new to us as well.

13. Alcon intends to submit the archive copy of this NDA partly in paper and partly in electronic format; paper archive and review copies for all 5 modules with the exception of case report forms, and patient listings being submitted only electronically in PDF format, SAS Transport files containing the biostatistical data will be provided on CD-ROM.

Seems fine, SAS transport file should be submitted to EDR.

The Sponsor indicated that the NDA is going to be submitted in two parts, the first part will be submitted during second quarter of 2002 and the second part will be submitted 120 days later. However, the PDUFA clock will be activated when all the components of the NDA have been submitted.

The discussion was concluded and the meeting adjourned.

Minutes Prepared By: S. Samanta _____

Minutes Concurred By: Janice Soreth _____

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Janice Soreth
3/29/02 03:56:02 PM

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>ALCON, INC. P.O. BOX 62 BOSCH 69 CH-6331 HUNENBERG SWITZERLAND</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>N021537</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(817) 568-6296</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>_____</p> <p>(APPLICATION NO. CONTAINING THE DATA.)</p>
<p>3. PRODUCT NAME</p> <p>ciprofloxacin 0.3% and dexamethasone 0.1% otic susp</p>	<p>6. USER FEE I.D. NUMBER</p> <p>4412</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

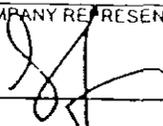
(See item 8, reverse side if answered YES)

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Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p>Seane D. Jones</p> 	<p>TITLE</p> <p>Assistant Director Regulatory Affairs</p>	<p>DATE</p> <p>August 23, 2002</p>
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