

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-537

CHEMISTRY REVIEW(S)



NDA 21-537

CiproDex[®] Otic Suspension

Alcon, Inc.

**Milton J. Sloan, Ph. D.
Division of Anti-Infective Drug Products (HFD-520)**

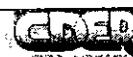


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Chemistry Review Data Sheet

1. NDA 21-537
2. REVIEW #: 1
3. REVIEW DATE: March 3, 2003
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Amendment (NC)	25-JUL-2002
Original	25-SEP-2002
Amendment (NC)	2-OCT-2002
Amendment (BZ)	19-NOV-2002
Amendment (E-mail, Desk Copy)	27-JUN-2003
Amendment (E-mail, Desk Copy)	03-JUL-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	25-SEP-2002
Amendment (BZ)	19-NOV-2003
Amendment (E-mail, Desk Copy)	27-JUN-2003

7. NAME & ADDRESS OF APPLICANT:

Name: ALCON, INC.
Address: P.O. Box 62, Bosch 69
H-6331 Hunenberg, Switzerland
Alcon Research, Ltd.
Representative: 6201 South Freeway
Fort Worth, Texas 76134-2099



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone: (817) 568-6296

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: CIPRODEX[®] Otic Suspension
- b) Non-Proprietary Name (USAN): Ciprofloxacin 0.3% and Dexamethasone 0.1% otic suspension
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 New Formulation
 - Submission Priority: S Standard Review, Substantially equivalent

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antibacterial/Anti Inflammatory

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: Ciprofloxacin hydrochloride monohydrate 0.3% w/v and Dexamethasone 0.1% w/v

13. ROUTE OF ADMINISTRATION: Transtympanic

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

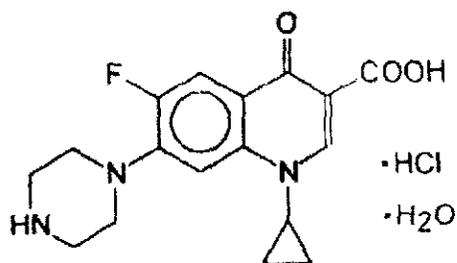
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

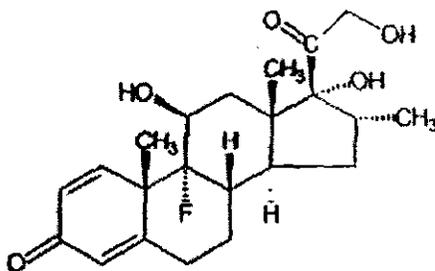
Ciprofloxacin Hydrochloride (1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate)



Molecular Formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular Mass: —

Dexamethasone (9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione)



Molecular Formula: $C_{22}H_{29}FO_5$

Molecular Mass: —



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE D	COMMENTS
	II	Bayer AG	Ciprofloxacin HCl	3	Adequate	20-Nov-2002 (D. Matecka)	Minor update since review to include additional data (May 16, 2003)
	II			3 and 4	Adequate	12-Jul-2002 (R. Permisohn)	Minor update since review 19-Apr-2002, LOA
	III			3 and 4	Adequate	27-Mar-2002 (Y. Lu)	1/24/02, LOA
	III			3	Adequate	13-Dec-1999 (S. Tso)	4/09/01, LOA
	III			3 and 4	Adequate	03-May-2002 (R. Frankewich)	2/21/96, LOA
	III			3 and 4	Adequate	17-Mar-2003 (Y. Lu)	3/06/02, LOA
	III			3 and 4	Adequate	11-Jul-2003	2/06/02, LOA
	V			4	N/A	N/A	
	V			4	N/A	N/A	

Action codes for DMF table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type I DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION/Status
NDA	19-537	Bayer, Cipro Tablets, Approved (10/22/87)
NDA	20-805	Alcon, Cipro HC Otic/ Approved (2/10/98)
NDA	20-369	Alcon, Ciloxan Ophthalmic Ointment/ Approved (3/30/98)
NDA	19-992	Alcon, Ciloxan Ophthalmic Drops/ Approved (12/31/90)
NDA	21-473	Bayer, Cipro XR Tablets 500 mg/ Approved (12/13/02)
NDA	20-780	Bayer, Cipro Suspension/ Approved (9/26/97)
NDA	50-592	Alcon, Tobradex (dexamethasone/tobramycin) Ophthalmic Suspension/ Approved (8/18/88).
NDA	50-616	Alcon, Tobradex (dexamethasone/tobramycin) Ophthalmic Ointment/ Approved (9/28/88).
NDA	13-422	Alcon, MAXIDEX Ophthalmic Suspension/
NDA	50-023	Alcon, MAXITROL Ophthalmic Suspension

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Acceptable	19-Mar-2003	J. D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Package sent to PHI-District Laboratory	03-Jun-2003	
OPDRA (DMETS)	No objections to Name		Denise Toyer, Carol Holquist, Jerry Phillips
EA	Categorical exclusion claimed	N/A	N/A
Microbiology	Approval	03-Feb-2003	Vinnie Pawar, Peter Cooney

19. ORDER OF REVIEW (OGD Only)

N/A

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:



The Chemistry Review for NDA 50-537

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approvable from the Chemistry, Manufacturing and Control perspective. Some pending concerns with the drug product acceptance criteria remain to be agreed upon.

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

None

II. Summary of Chemistry Assessments

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

CIPRODEX Otic Suspension is a sterile, stable, adequately preserved suspension containing 0.3% w/v ciprofloxacin hydrochloride, monohydrate (equivalent to 0.3% w/v ciprofloxacin hydrochloride or 0.3% w/v ciprofloxacin as base) and 0.1% w/v dexamethasone. Ciprofloxacin is a broad-spectrum antibacterial agent and dexamethasone is an anti-inflammatory steroid.

CIPRODEX Otic Suspension will be packaged in 5 mL natural polyethylene and natural DROP-TAINER® dispenser bottles fitted with natural dispensing plugs and white polypropylene (PP) closures.

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

The proposed indications for CIPRODEX Otic Suspension are for the topical treatment of otic bacterial infections and inflammation (Acute Otitis Media with Tympanostomy Tubes and Acute Otitis Externa).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has satisfactorily demonstrated via CMC data submitted in the application that this new formulation is stable throughout the two year shelf life of the



CHEMISTRY REVIEW



Executive Summary Section

drug product. The manufacturing sites have been found acceptable with the Office of Compliance. The proposed specifications have not however, been found adequate and suitable for a quality drug product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name: Milton J. Sloan, Ph. D.

Date: July 1, 2003

Chemistry Team Leader Name: James D. Vidra, Ph. D.

Date:

C. CC Block

HFD-520/Archival

HFD-520/Nguyen/PM

HFD-520/Smith/MO

HFD-520/Sloan/CHM

HFD-520/Ellis/PhmTox

HFD-520/Silver/Micro

HFD-520/Jiang/Stat

HFD-520/Vidra/TLCHM

HFD-830/Chen/DivDir

**APPEARS THIS WAY
ON ORIGINAL**

99 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/

Milton Sloan
7/16/03 11:00:47 AM
CHEMIST

Jim Vidra
7/16/03 01:44:54 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21537/000
Stamp: 25-SEP-2002 Regulatory Due: 25-JUL-2003
Applicant: ALCON LABORATORIES INC
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

Priority: 3S
Action Goal:
Brand Name: CIPRODEX OTIC SUSPENSION
Established Name:
Generic Name: CIPROFLOXACIN/DEXAMETHASONE
OTIC SUSPENS
Dosage Form: SUS (SUSPENSION)
Strength: CIPRO & DEX 0.1%

Org Code: 520
District Goal: 26-MAY-2003

FDA Contacts: D. NGUYEN (HFD520) 301-827-2125 , Project Manager
M. SLOAN (HFD-520) 301-827-2174 , Review Chemist
J. VIDRA (HFD-540) 301-827-2065 , Team Leader

Overall Recommendation:

ACCEPTABLE on 19-MAR-2003 by J. D AMBROGIO (HFD-322) 301-827-9054

Establishment: 1610287
ALCON LABORATORIES INC
6201 SOUTH FREEWAY
FORT WORTH, TX 76115

DMF No:
AADA No:

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-MAR-2003
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-NOV-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment: 9610496
BAYER AG
GESCHAFTSBEREICH PHARMA
WUPPERTAL-ELBERFELD, , GM D-4

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-NOV-2002

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

**APPEARS THIS WAY
ON ORIGINAL**