

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20 - 369**

MICROBIOLOGY REVIEW(S)

**REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

**Microbiologist's Review #3 of NDA 20-369
Addendum to Pending Application
December 11, 1997**

A. 1. APPLICATION NUMBER: 20-369

APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134-2099

2. PRODUCT NAMES: Ciloxan ophthalmic ointment (ciprofloxacin hydrochloride)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.3%
ciprofloxacin ophthalmic ointment tube (3.5 g) for multiple use.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Treatment of bacterial conjunctivitis

B. 1. DATE OF INITIAL SUBMISSION: July 9, 1997

2. AMENDMENT: November 10, 1997

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: December 11, 1997

5. DATE OF CONSULT REQUEST: December 11, 1997

C. REMARKS:

This addendum is to reverse the recommendation for approval by Microbiologist's Review #2. The Not Approvable conclusion is based on the new information provided by the FDA inspection. The drug product is manufactured at the Alcon's manufacturing facility in Humancao, Puerto Rico.

DEC 17 1997

D. CONCLUSIONS:

- The amendment is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "Review Notes" and in the "List of Microbiology Deficiencies and Comments".

12/11/97
Brenda Uratani, Ph.D.
Review Microbiologist

PAC 12/12/97

cc:

NDA 20-369 Addendum
HFD-550/ Div. File
HFD-805/ Uratani
HFD-550/CSO/ Gorski
HFD-550/Chemist/Uppoor
drafted by: Brenda Uratani, 12/11/97
R/D initialed by P. Cooney, 12/11/97

SEP 23 1997

**REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

Microbiologist's Review #1 of NDA 20-369
Amendment to Pending Application
September 16, 1997

A. 1. **APPLICATION NUMBER:** 20-369

APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134-2099

2. **PRODUCT NAMES:** Ciloxan ophthalmic ointment (ciprofloxacin hydrochloride)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 0.3%
ciprofloxacin ophthalmic ointment tube (3.5 g) for multiple use.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Treatment of bacterial conjunctivitis

B. 1. **DATE OF INITIAL SUBMISSION:** July 9, 1997

2. **AMENDMENT:**

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** July 28, 1997

5. **DATE OF CONSULT REQUEST:** July 18, 1997

C. **REMARKS:**

Ciloxan is a synthetic, sterile, multiple dose, antimicrobial ophthalmic ointment for topical use. Ciprofloxacin, a fluoroquinolone antibacterial agent, is active against a broad spectrum of gram-positive and gram-negative bacteria. The bacterial action of ciprofloxacin results from interference with bacterial DNA gyrase.

The original submission was not approved as submitted. This is an amendment to provide additional clinical studies and microbiology CMC section.

D. CONCLUSIONS:

The submission does not contain sufficient information to assure the sterility and safety of the drug product. The NDA is, therefore, not recommended for approval as submitted. Specific comments are provided in "Review Notes" and in the "List of Microbiology Deficiencies and Comments".

9/16/97

Brenda Uratani, Ph.D.
Review Microbiologist

PHC 9/23/97

cc:

NDA 20-369 Amendment
HFD-550/ Div. File
HFD-805/ Uratani
HFD-550/CSO/ D'Anni Gunter
drafted by: Brenda Uratani, 9/16/97
R/D initialed by P. Cooney, 9/16/97

**REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

**Microbiologist's Review #3 of NDA 20-369
Addendum to Pending Application
December 11, 1997**

- A. 1. **APPLICATION NUMBER:** 20-369
- APPLICANT:** Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134-2099
2. **PRODUCT NAMES:** Ciloxan ophthalmic ointment (ciprofloxacin hydrochloride)
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 0.3%
ciprofloxacin ophthalmic ointment tube (3.5 g) for multiple use.
4. **METHOD(S) OF STERILIZATION:**
5. **PHARMACOLOGICAL CATEGORY:** Treatment of bacterial conjunctivitis
- B. 1. **DATE OF INITIAL SUBMISSION:** July 9, 1997
2. **AMENDMENT:** November 10, 1997
3. **RELATED DOCUMENTS:**
4. **ASSIGNED FOR REVIEW:** December 11, 1997
5. **DATE OF CONSULT REQUEST:** December 11, 1997
- C. **REMARKS:**

This addendum is to reverse the recommendation for approval by Microbiologist's Review #2. The Not Approvable conclusion is based on the new information provided by the FDA inspection. The drug product is manufactured at the Alcon's manufacturing facility in Humacao, Puerto Rico.

D. CONCLUSIONS:

- The amendment is not recommended for approval on the basis of sterility
- assurance. Specific comments are provided in "Review Notes" and in the "List of
Microbiology Deficiencies and Comments".

12/11/97
Brenda Uratani, Ph.D.
Review Microbiologist

PAC 12/12/97

cc:

NDA 20-369 Addendum
HFD-550/ Div. File
HFD-805/ Uratani
HFD-550/CSO/ Gorski
HFD-550/Chemist/Uppoor
drafted by: Brenda Uratani, 12/11/97
R/D initialed by P. Cooney, 12/11/97

MAR 23 1998

**REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

Microbiologist's Review #4 of NDA 20-369/Amendment
March 23, 1998

A. 1. **APPLICATION NUMBER:** 20-369

APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134-2099

2. **PRODUCT NAMES:** Ciloxan ophthalmic ointment (ciprofloxacin hydrochloride)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 0.3%
ciprofloxacin ophthalmic ointment tube (3.5 g) for multiple use.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Treatment of bacterial conjunctivitis

B. 1. **DATE OF INITIAL SUBMISSION:** July 9, 1997

2. **AMENDMENT:** November 10, 1997; January 30, 1998, March 19, 1998.

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** March 19, 1998

5. **DATE OF CONSULT REQUEST:** March 19, 1998

C. **REMARKS:**

The amendment responds to deficiencies in Microbiology Review #3 (December 11, 1997). The questions from the "List of Microbiology Deficiencies and Comments" have been copied into the "Review Notes" section of this review and the responses are individually reviewed.

D. CONCLUSIONS:

Satisfactory answers were submitted in response to Microbiology deficiencies. The application is recommended for approval with regard to microbiology, contingent upon satisfactory inspection of the manufacturing facilities from FDA Compliance.

3/23/98

Brenda Uratani, Ph.D.
Review Microbiologist

PK 3/23/98

cc:

NDA 20-369 Addendum
HFD-550/ Div. File
HFD-805/ Uratani
HFD-550/CSO/ Gorski
HFD-550/Chemist/Uppoor
drafted by: Brenda Uratani, 3/23/98
R/D initialed by P. Cooney, 3/23/98

115
OCT 24 1997

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

Consultative Review for HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

Requestor: Lori Gorski, CSO HFD-550

Date of Request: September 16, 1997

Reason for Request: Microbiological Review for safety and efficacy

NDA #: 20-369

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 20-JUN-97
CDER RECEIPT DATE: 24-JUN-97
REVIEW ASSIGN DATE: 29-SEP-97
REVIEW COMPLETE DATE: 17-OCT-97

SPONSOR:

ALCON LABORATORIES, INC.
6201 South Freeway
Fort Worth, Texas 76134-2099

CONTACT PERSON:

Cheryl B. Anderson, Pharm. D.
Manager Regulatory Affairs
Phone Number: (817) 551-4325

SUBMISSION REVIEWED: Amendment to Pending Application

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Treatment of bacterial conjunctivitis

DOSAGE FORM: Sterile ophthalmic ointment: 3.5 grams/tube

DRUG PRODUCT NAME

PROPRIETARY:

CILOXAN™ Ophthalmic Ointment

NONPROPRIETARY/USAN:

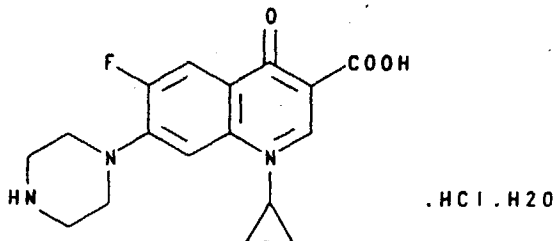
Ciprofloxacin hydrochloride ophthalmic ointment

CHEMICAL NAME:

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride, monohydrate.

NDA 20-369
ALCON LABORATORIES, INC.
CIPROFLOXACIN OPHTHALMIC OINTMENT

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$
MOLECULE WEIGHT: 385.82

SUPPORTING DOCUMENTS:

BACKGROUND:

This amendment is a response to the not approvable letter issued on May 17, 1994. When this application originally was submitted the sponsor proposed indications of bacterial conjunctivitis and bacterial corneal ulcers.

The applicant has performed a prospective, randomized placebo controlled trial using CILOXAN Ophthalmic Ointment in the treatment of bacterial conjunctivitis. In addition, CILOXAN Ophthalmic Ointment was evaluated in pediatric patients. Based on these additional studies the applicant seeks approval to use the ointment only in the treatment of bacterial conjunctivitis.

NDA 20-369

ALCON LABORATORIES, INC.

CIPROFLOXACIN OPHTHALMIC OINTMENT

REMARK(S): Alcon Laboratories already has an approved NDA for ciprofloxacin ophthalmic solution. The microbiology has, therefore, already been approved for ciprofloxacin use as an ophthalmic. The labeling for this product is similar to that approved for the ophthalmic solution, except that references to an indication for corneal ulcers has been deleted. I believe that this labeling should be updated and have indicated this in my review.

CONCLUSIONS and/or RECOMMENDATIONS: From the microbiology standpoint this drug product should be approved with changes in the microbiology section of the package insert. The sponsor should be notified of the changes in the microbiology section of the package insert as indicated on pages 50-54 of this review.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-369
ALCON LABORATORIES, INC.
CIPROFLOXACIN OPHTHALMIC OINTMENT

Peter A. Dionne
Microbiologist, HFD-590

CONCURRENCES:

HFD-590/DIV DIR
HFD-590/TLMicro

Signature 10/29/97 Date
Signature 10/24/97 Date

CC:
HFD-590/Original NDA #20-369
HFD-590/Division File
HFD-590/TLMicro/LUtrup
HFD-590/Micro/PDionne
HFD-590/CSO/PFogarty
HFD-550/MO/WChambers
HFD-550/CSO/LGorski
HFD-550/Pharm/CChen
HFD-550/Chem/RUppoor