CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-369

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

FEDERAL EXPRESS AWB 7196496042

Alcon LABORATORIES

May 21, 1993

ORIGINAL

ALCON LABORATORIES INC
6201 SOUTH FREEWAY
FORT WORTH TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Food & Drug Administration
Central Document Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Joanne B. Marriott
Associate Director
Regulatory Affairs

RE: ORIGINAL NEW DRUG APPLICATION (NDA)
CIPROFLOXACIN HCL OPHTHALMIC OINTMENT 0.3% AS BASE

Dear Sir or Madam:

We are submitting a NDA for Ciprofloxacin HCl Ophthalmic Ointment with proposed indication for use in the treatment of bacterial conjunctivitis and corneal ulcers.

The applications consists of an Archival and a Technical Review copy. The Archival copy consists of 15 volumes and an Index is located in Volume 1. The Technical Review copy consists of volumes for:

Chemistry
Pharmacology
Human Pharmacokinetics
Microbiology
Clinical Data
Biostatistics

Tradename: Ciloxan® Ophthalmic Ointment

Pagination: The document is consecutively paginated in the lower right hand corner. The page number is made up of two parts, i.e. page 7-100 represents the item number corresponding the Microbiology Section (Form 356h) and "100" is the consecutive number within the Microbiology Section.

CANDA: A desk copy is being provided under separate cover directly to the Division of Anti-Infective Drug Products consisting of the Index, Summary, Labeling, Clinical Data and Biostatistical reports in WordPerfect 5.1 on 3.5 inch micro diskettes. The Case Report Tabulations are being provided on Lotus 1-2-3 spreadsheets on the same media.

Additionally, a volume consisting of 35 mm slides of corneal ulcer from Protocol C-90-85 "A Clinical Evaluation of the Efficacy and Safety of Ciprofloxacin Ophthalmic Ointment 0.3% in Treating Bacterial Corneal Ulcers" is being provided under separate cover directly to the Division.

NDA 20-369

Joanne B. Marriott
Associate Director
Regulatory Affairs
Alcon Laboratories, Inc.
5201 South Freeway
Fort Worth, TX 76134

JUN 18 1993

Dear Ms. Marriott:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ciprofloxacin HCl Ophthalmic Ointment

Date of Application: May 21, 1993

Date of Receipt: May 24, 1993

Our Reference Number: NDA 20-369

Unless we find the application not acceptable for filing, the filing date will be July 24, 1993.

Please begin any communication concerning this application by citing the NDA number listed above. Should you have any questions conerning the NDA, please contact:

Mrs. Regina Joyce
Project Manager
(301) 443-0335

Sincerely yours,

6/15/93

James D. Bona, R.Ph.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
ORIG. NDA 20-369
HFD-520
HFD-520/MO/JCarreras
HFD-520/CHEM/
HFD-520/PHARM/LBuko
HFD-521/PMS/RJoyce 6/15/93
KKonkolewski/6/7/93
F/T:

93

EDERAL EXPRESS
WB 7144263125

ORIGINAL

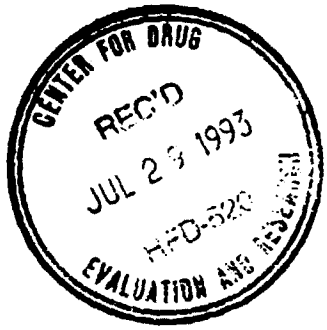
NDA ORIG AMENDMENT
Bm

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

ıly 28, 1993



od and Drug Administration
vision of Anti-Infective Drug Products HFD-520
nter for Drug Evaluation and Research
cument Control Room 12B30
00 Fishers Lane
ckville, Maryland 20857

: **NDA 20-369**
CILOXAN (Ciprofloxacin Ophthalmic Ointment USP)

ar Sir or Madam:

erence teleconference of July 22, 1993 with Dr. Chambers, Dr. Carreras and Regina
ce find enclosed the case report forms for the protocols associated with Ciloxan
tment.

here are any further questions, please do not hesitate to contact the undersigned
ctly at (817) 568-6296.

erely,

Joanne B. Marriott

ıne B. Marriott

ORIGINAL

MAIL P 168 958 479
ECEIPT REQUESTED

NEW CORRESPONDENCE

Alcon LABORATORIES

ALCON LABORATORIES, INC
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

)93

)rug Administration
Anti-Infective Drug Products HFD-520
Drug Evaluation and Research
Control Room 12B30
:rs Lane
Maryland 20857

20-369
)XAN (Ciprofloxacin Ophthalmic Ointment, USP)

Madam:

)ment in a follow-up to the telephone conference of July 22, 1993 with Wiley M.D., Juan Carreras, M.D. and Regina Joyce regarding the Placebo study 8-94) submitted under the above referenced applications.

ed information is provided as a written response to the inquiry relating to the)f Investigator 1523 (Dr. M. Mintz).

e any further questions, please do not hesitate to contact the undersigned (817) 568-6296.

B. Marriott

Marriott

NDA [illegible] AMENDMENT

BC

CERTIFIED MAIL P 378 612 339
RETURN RECEIPT REQUESTED

ORIGINAL

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

August 20, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
CILOXAN (ciprofloxacin HCl ophthalmic ointment, USP)
AMENDMENT

Dear Sir or Madam:

In response to teleconference of July 22, 1993 find enclosed in duplicate the revised Environmental Assessment for the above referenced application.

If there are any further questions, please do not hesitate to contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

Joanne B. Marriott

...RTIFIED MAIL P 168 958 472
...TURN RECEIPT REQUESTED

ORIGINAL

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

...gust 31, 1993

...d and Drug Administration
...ision of Anti-Infective Drug Products HFD-520
...nter for Drug Evaluation and Research
...ument Control Room 12B30
...0 Fishers Lane
...kville, Maryland 20857

NDA 20-369
CILOXAN (ciprofloxacin HCl Ointment)

...r Dr. Shetty:

...conversation of August 31, 1993, find enclosed a copy of the USP Supplement V for ...ofloxacin HCl.

...ere are any further questions, please do not hesitate to contact the undersigned ...tly at (817) 568-6296.

...erely,

Joanne B. Marriott

...ne B. Marriott

9/9/93

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 0 8 1993
HFD-520

NDA ORIG AMENDMENT
AM

CERTIFIED MAIL P 168 958 434
RETURN RECEIPT REQUESTED

ORIGINAL

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

October 4, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
CILOXAN (Ciprofloxacin HCl Ointment)

Dear Sir or Madam:

Attached find a copy of the amended CMR for Protocol C-88-94 "A Multiclinic Evaluation of the Efficacy and Safety of Ciprofloxacin Ophthalmic Ointment versus Placebo in Treating Bacterial Conjunctivitis."

If there are any further questions, please do not hesitate to contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

Joanne B. Marriott

Desk Copy: J. Carreras, M.D.

NDA 20-369

Joanne B. Marriott
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

OCT 21 1993

Dear Ms. Marriott:

Reference is made to your New Drug Application (NDA), and to your amendment dated October 4, 1993, received by the Food and Drug Administration (FDA) on October 6, 1993, for Ciloxan Ointment.

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 60 additional days will be required for its review.

The new due date is January 19, 1994.

If questions arise concerning this NDA, please contact Mrs. Regina Joyce, of the Project Management Staff at 301-443-0335.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
ORIG. NDA 20-369
HFD-520
HFD-520/SMO/WChambers WAC 10/18/93
HFD-520/MO/TCarreras
HFD-520/CHEM/BShetty
HFD-520/PHARM/ROsterberg
HFD-521/PMS/RJoyce RJ 10/18/93
KKonkolewski/10/18/93 KK 10/18/93
F/T:

Quad

NDA ORIG AMENDMENT
BM

Alcon
LABORATORIES

ALCON LABORATORIES, INC
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Booze Messenger Service
Federal Express A/B 8017323764

November 5, 1993

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products HFD-520
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
CILOXAN® (ciprofloxacin HCl 0.3%) Ophthalmic Ointment

Dear Sir or Madam:

Please find enclosed a biostatistical report comparing the efficacy in each of the two clinical studies of Ciloxan ointment to standard therapy historical control studies and Ciloxan solution studies for treatment of bacterial corneal ulcers.

This additional information was requested by Dr. T. Carreras in the telephone conference of October 13, 1993.

A desk copy, in addition to Archival, Clinical and Statistical review copies, is provided. The report is also provided on one 3.5 inch PC diskette in WordPerfect.

If there are any further questions, please do not hesitate to contact the undersigned directly at 817/568-6296.

Sincerely,

Joanne B. Marriott

Joanne B. Marriott
Associate Director
Regulatory Affairs

JBM/db
Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 08 1993
HFD-52

ORIGINAL

NDA ORIG AMENDMENT

IED MAIL P 168 958 496
N RECEIPT REQUESTED

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

nber 11, 1993

and Drug Administration
on of Anti-Infective Drug Products HFD-520
er for Drug Evaluation and Research
iment Control Room 12B30
) Fishers Lane
:ville, Maryland 20857

NDA 20-369
CILOXAN (ciprofloxacin ophthalmic ointment)

ar Sir or Madam:

is amendment which includes additional photographs from the corneal ulcer study, otocol C-90-85 is being submitted in response to a request by Dr. Wiley Chambers and . Juan Carreras via a telephone conference on July 22, 1993.

: the request of FDA we contacted investigators to determine if any entry photographs bacterial corneal ulcers that were treated with ciprofloxacin ointment in the open-label udy (C-90-85) were inadvertently not submitted.

n response to our inquiry seven additional photographs from four investigators were rovided and, one set of the seven slides are being submitted for incorporation to the ending NDA.

f there are any further questions, please do not hesitate to contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

Joanne B. Marriott

ORIGINAL

Alcon LABORATORIES

Joanne B. Marriott

Federal-Express
A/B 8017323742

December 15, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
CILOXAN (ciprofloxacin HCl) ophthalmic Ointment 0.3% as Base
Biostatistical Response

Dear Sir or Madam:

This amendment is submitted in response to a teleconference request of December 7, 1993 from Dr. Juan Carerras for the clarification of a biostatistical analyses amendment submitted November 5, 1993.

In addition, Dr. Carerras requested that we provide mean baseline values for the six important clinical signs.

The contents of this amendment were discussed with Dr. Carerras on December 10, 1993 and respond fully to his request.

If there are any questions regarding this application please contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

JBM
Enclosure

Facsimile to J. Carreras 12/15/93

FEDERAL EXPRESS
AWB 7144263372

ORIGINAL

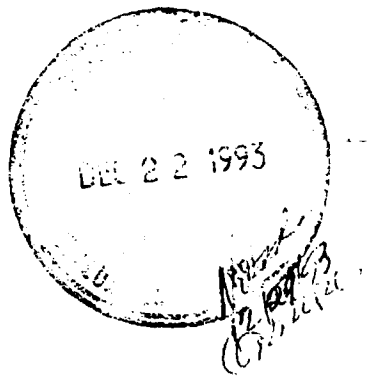
Alcon LABORATORIES

ALCON LABORATORIES, INC
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

December 21, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857



RE: NDA 20-369
CILOXAN (ciprofloxacin) Ophthalmic Ointment

Dear Sir or Madam:

This amendment is submitted in response to the chemistry questions listed in a copy of a draft letter to the sponsor of chemistry deficiencies received on October 20, 1993.

If there are any further questions, please do not hesitate to contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

Joanne B. Marriott

FEDERAL EXPRESS
AWB 7144263361

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

January 5, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
CILOXAN (ciprofloxacin ophthalmic ointment)

Dear Sir or Madam:

As requested by Dr. R. Srinivasan, Division of Biomedics in a teleconference of January 4, 1994, enclosed is a diskette containing the Study 1 and Study 2 PC SAS Version 6.04 datasets for all culture positive patients for the above referenced application. Also included are pages listing the contents of the two datasets on the diskette as well as the PC SAS Version 6.04 formats needed.

If there are any further questions, please do not hesitate to contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

Joanne B. Marriott

FEDERAL EXPRESS
AWB 7144263346

ORIGINAL

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Joanne B. Marriott
Associate Director
Regulatory Affairs

January 20, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
CILOXAN (ciprofloxacin HCl ophthalmic ointment)

Dear Sir or Madam:

The attached information is submitted in response to a telephone request of January 14, 1994 from Dr. E. Ross Pierce, Division of Scientific Evaluation, regarding a directed inspection of the placebo study (Protocol C-88-94) filed under the above referenced application.

If there are any further questions, please do not hesitate to contact the undersigned directly at (817) 568-6296.

Sincerely,

Joanne B. Marriott

Desk copy: E. Ross Pierce
Division of Scientific Evaluation
Food and Drug Administration
Metro Park North I
7520 Standish -- Room 125
Rockville, Maryland 20855

NDA 20-369

Joanne B. Marriott
Associate Director, Regulatory Affairs
Alcon Laboratories, Incorporated
6201 South Freeway
Forth Worth, TX 76134-2099

JAN 28 1994

Dear Ms. Marriott:

Reference is made to your new drug application (NDA) and to your amendment dated December 21, 1993, received by the Food and Drug Administration (FDA) on December 22, 1993, for Ciloxan Ophthalmic Ointment.

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 60 additional days will be required for its review.

The new due date is February 20, 1994.

If questions arise concerning this NDA, please contact Mrs. Regina Joyce of the Project Management Staff at 301-443-0257.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
ORIG. NDA 50-369
HFD-520
HFD-520/SMO/WChambers WRC 1/18/94
HFD-520/MO/JCarreras
HFD-520/CHEM/Shetty
HFD-521/PMS/RJoyce RJ 1/14/94
KKonkolewski/1/13/94
F/T:

ORIGINAL

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450 TELEX 758320

Certified Mail P 226 713 207
Return Receipt Requested

May 18, 1994

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products, HFD-540
Office of Drug Evaluation II
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-369
Ciloxan (ciprofloxacin) Ophthalmic Ointment
Intent to File Amendment

Dear Dr. Wilkin:

In reference to the not approvable letter dated May 17, 1994, please be advised that we intend to file an amendment responding completely to the stated deficiencies.

We plan to request through Mrs. Regina Joyce an informal conference with the Division to discuss the deficiencies and the steps necessary to secure approval.

Sincerely,

Robert E. Roehrs, Ph.D.

RER/db
Enclosure

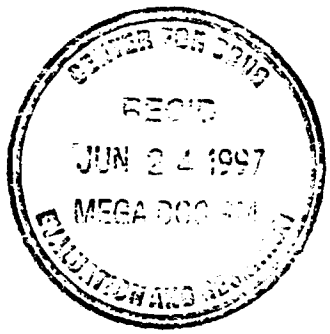
AirBorne Express 2204147466
c/o Booze Messenger Service

ALCON LABORATORIES, INC ORIG AMENDMENT
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

June 20, 1997

Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Document Control Room
Rockville, Maryland 20850

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager



RE: **NDA 20-369**
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Amendment To Pending Application

Dear Madam or Sir:

In communication dated May 17, 1994, the FDA advised that the above referenced application was not approvable. The letter stated the following:

A prospective, randomized placebo controlled trial has been conducted 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, Alcon now seeks approval to use the drug product only in the treatment of bacterial conjunctivitis. Alcon withdraws its requests for approval to use the drug product in the treatment of bacterial corneal ulcers without prejudice for future filing.

In addition, an *in vitro* study was conducted to demonstrate that the pilot batches manufactured in Process Development are equivalent to the production batches. The results are submitted herein.

This submission consists of an archival and technical review copy. The archival copy consists of 16 volumes. The technical review copies are provided for the Chemistry, Manufacturing, and Controls, Microbiology, Clinical Data and Biostatistics sections. An additional copy of the Microbiology technical section is provided as requested.

The information contained in this amendment replaces the sections submitted in the original application, unless otherwise noted.

The submission is consecutively paginated in the lower right hand corner. The page number is made up of two parts. An example is page "0001." The "3" represents the item number corresponding to Part 3, Chemistry, Manufacturing and Controls section (Form 356h) and "0001" is the consecutive page number within the CMC section. Four copies of the draft labeling are provided.

An electronic version will be provided under separate cover directly to the Division of Analgesic, Anti-Inflammatory and Ophthalmic Drug Products consisting of the Summary, Labeling, Clinical Data and Biostatistical Reports in WordPerfect 5.1. These diskettes are being sent to the attention of Lissante LoBianco, Project Manager.

Alcon certifies that a copy of the Chemistry, Manufacturing, and Controls section of the submission has been sent to the FDA District Office in Dallas, Texas.

Further, Alcon acknowledges that the application cannot be approved until satisfactory Establishment Inspection Reports have been received for the facilities involved in the manufacture and packaging of the drug product.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325. Please address all future correspondence to the undersigned.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

Certified Mail Z 047 937 215
Return Receipt Requested

Alcon
LABORATORIES

ALCON LABORATORIES, INC
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

July 9, 1997

Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Document Control Room
Rockville, Maryland 20850

RE: NDA 20-369
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Amendment To Pending Application

Dear Madam or Sir:

An amendment to the above referenced application was submitted on June 20, 1997. Following you will find an electronic version of the same submission in WordPerfect 5.1 on CD-ROM and the patient listings for clinical studies C-93-88 and C-91-29 in Lotus spreadsheets on diskettes. Per your request, two additional desk copies of the summary are being provided for the microbiologist and pharmacologist reviewers.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

D'Anni Gunter, Project Manager, Room N317 (including 2 desk copies, CD-ROM, and diskettes)

Post-it™ brand fax transmittal memo 7671 | # of pages ▸

To Lora Gorski	From
Co.	Co.
	Phone #
Fax # 301 827 2531	Fax #

Aug 5, 1997 correspondence fax

Alcon
LABORATORIES

ALCON LABORATORIES, INC
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Michael Weintraub, M.D.
Acting Director
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA 20-369 Ciloxan® (ciprofloxacin hydrochloride ophthalmic ointment)
Amendment to a Pending Application

Dear Sir/Madam:

In response to Ms. Gunter's telephone request of July 25, 1997, please find attached the following information:

1. The Case Report Forms with annotated SAS variable names for C9388, C9129 and C8824 (see CRFs).

2. SAS programs and datasets used for efficacy analysis of protocols C9388, C9129 and C8824 (provided on a diskette).

3. Documentation of SAS program, dataset used and CMR Tables generated by the SAS program is given below:

Protocol	SAS Program	Dataset	CMR Table Information
C9388	C9388SAS	C9388.SSD	Tables 3-10, 12b-18
C9129	C9129.SAS	C9129.SSD	Tables 3-14, 17-30
C9924	C8824C.SAS	C8824C.DAT	Tables 3-4, 8-25

Please contact Cheryl Anderson at (817) 551-4325 or the undersigned at (817) 568-6296 should you require additional information.

Sincerely,

Susan H. Caballa
Susan H. Caballa
Assoc. Director
Regulatory Affairs

310.fda

Certified Mail Z 047 939 746
Return Receipt Requested

ORIG AMENDMENT

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

September 2, 1997

Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Document Control Room
Rockville, Maryland 20850

RE: NDA 20-369
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Amendment To Pending Application

Dear Madam or Sir:

An amendment to the above referenced application was submitted on June 20, 1997. Following you will find toxicology reports for the product packaging that are referred to on page 3-0252. The toxicology reports were inadvertently omitted.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

D'Anni Gunter, Project Manager, Room N317

AirBorne Express 8383741052

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

September 24, 1997

Wiley Chambers, M.D., Deputy Director
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Food and Drug Administration
CDER, HFD-550
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

Laura,
Micro data
sets you
requested
D'Anne

RE: NDA 20-369
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Amendment

Dear Dr. Chambers,

Per Lt. Commander Gunter's request, SAS datasets of the microbiologic data for each of the three clinical protocols (C-88-24, C-91-29, and C-93-88) are provided.

In addition, a desk copy of the pertinent microbiology and clinical sections from the amendment dated June 20, 1997 and the original application were provided September 19, 1997 for the Clinical Microbiology consult.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

Lt. Commander D'Anni Gunter, Project Manager, Room N317 (electronic diskette included)

Certified Mail Z 047 939 767
Return Receipt Requested

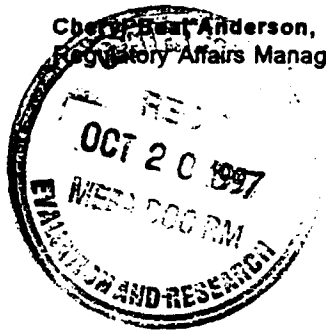
BL
ORIG AMENDMENT

October 14, 1997

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager



Division of ~~Analgesic~~, Anti-Inflammatory and
Ophthalmic Drug Products
Food and Drug Administration
CDER, HFD-550, Room N314
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: **NDA 20-369**
CILOXAN® Ophthalmic Ointment
(ciprofloxacin HCl ophthalmic ointment)
Amendment to Pending Application - Revised Draft Labeling

Dear Madam or Sir:

Following you will find revised labeling for the label and carton for the above referenced drug product. The original submission, as amended June 20, 1997, read as follows:

"**Ciloxan®**
Ciprofloxacin HCl Ophthalmic Ointment
Contains ciprofloxacin HCl equivalent to 0.3% ciprofloxacin"

It is now revised to:

"**Ciloxan®**
(ciprofloxacin HCl ophthalmic ointment)
0.3% as base"

The change was made to be consistent with the package insert and recent FDA recommendations to use lower case for the established name.

The agency's time in the review of this submission is appreciated. If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

Certified Mail Z 047 939 782
Return Receipt Requested

ALCON LABORATORIES, INC
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

November 10, 1997

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

RE: **NDA 20-369**
CILOXAN Ointment
(ciprofloxacin hydrochloride opthalmic ointment, 0.3% as base)
Amendment To Pending Application - Microbiology Deficiencies

Dear Madam or Sir:

In FDA communication faxed on October 15, 1997, microbiology deficiencies were identified for the above referenced application. Following you will find Alcon's response to all issues identified.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk copy: Lori Gorski, Project Manager

BB
ORIG AMENDMENT
ORIGINAL

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

November 19, 1997

Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Food and Drug Administration
CDER, HFD-550, Room N314
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: **NDA 20-369**
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Amendment to Pending Application

Dear Madam or Sir,

The National Environmental Policy Act; Revisions of Policies and Procedures; Final Rule was issued July 29, 1997 and became effective August 28, 1997. Under 21 CFR 25.15(d), Alcon hereby amends the above referenced application and claims categorical exclusion under 25.31(a):

> "Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety."

If there are any questions regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

Certified Mail Z 047 939 792
Return Receipt Requested

Airborne Express 9768739153

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

November 24, 1997

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

Dr. Raj Uppoor
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Food and Drug Administration
CDER, HFD-550
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-369
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Amendment to Pending Application – Chemistry Response

Dear Dr. Uppoor,

Following please find Alcon's response to FDA fax communication dated 11/21/97 regarding the above referenced application. The response addresses all chemistry issues raised and as agreed in our 11/21/97 teleconference with you and Ms. Lori Gorski, Project Manager.

If there are any questions regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk copy: Ms. Lori Gorski, Project Manager, N317

Certified Mail Z 047 937 896
Return Receipt Requested

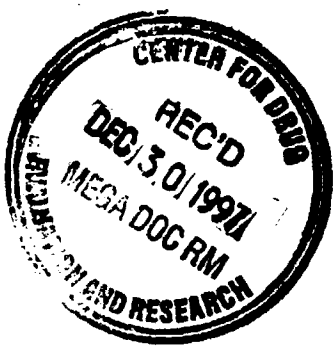
NEW CORRESP

DUPLICATE

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

December 23, 1997



Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Food and Drug Administration
CDER, HFD-550, Room N314
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-369
CILOXAN Ophthalmic Ointment
(ciprofloxacin hydrochloride ophthalmic ointment)
Intent to Amend

Dear Dr. Chambers,

Reference is made to FDA communication dated December 23, 1997 which the agency advises that the above referenced application is approvable. Please be advised that Alcon intends to amend this application as soon as possible with the requested information.

If there are any questions regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl B. Anderson, Pharm.D.
Manager, Regulatory Affairs

January 30, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Re: NDA 20-369
CILOXAN (ciprofloxacin hydrochloride ophthalmic ointment)
Amendment to Pending Application

Dear Dr. Chambers,

Reference is made to FDA communication dated December 23, 1997. Therein, the FDA advised that the above referenced application is approvable. Following please find Alcon's response to each deficiency comment.

Four copies of draft labeling are provided in this amendment. The labeling is identical to that provided by the FDA with the following exceptions:

1. Due to space constraints, the trade name is shown as "CILOXAN" on the label and carton. The trade name is similarly presented on the package insert. The dosage form is stated in the established name and is repeated again immediately following the established name.

2. An additional statement has been added to the WARNINGS section, "FOR TOPICAL OPHTHALMIC USE ONLY."

3. An additional section has been added to the PRECAUTIONS section, "Information For Patients: Do not touch tip to any surface as this may contaminate the ointment."

Alcon believes that the addition of the two safety statements increases the safe use of the product, while providing consistency with other Alcon products.

Per 21 CFR 314.50(d)(vi)(b), a safety update is to be provided. Please be advised that there is no new safety information to report at this time.

Lastly, the introductory promotional material that is proposed for use with the drug product will be submitted when available.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk copy: Wiley Chambers, M.D.
Lori Gorski, Project Manager

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
24 May 93	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
520	20-369

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon Laboratories, Inc.	
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO** *(Include Area Code)*
6201 South Freeway Fort Worth, Texas 76134	(817) 568-6296
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Ciprofloxacin HCl Ophthalmic Ointment	Ciloxan Ophthalmic Ointment

CODE NAME *(If any)*	CHEMICAL NAME

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Ointment	Ocular	.3%

PROPOSED INDICATIONS FOR USE

NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, **NEW DRUG OR ANTIBIOTIC APPLICATIONS** *(21 CFR Part)*, **AND DRUG MASTER FILES** *(21CFR 314 420)* **REFERRED TO IN THIS APPLICATION:**

1993
RESEARCH

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT (OTC)

MAR 1 1994

NDA 20-369

SUBMISSION DATE: May 21, 1993
January 12, 1994

CILOXAN™ Ophthalmic Ointment
(Ciprofloxacin HCl) 0.3% as Base
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: New Drug Application **Code 3S**

I. SYNOPSIS:

The sponsor submitted NDA 20-369 on May 21, 1993 for Ciloxan™ Ophthalmic Ointment. On January 12, 1994, an Admendment to NDA 20-369 was submitted by the sponsor in response to a Biopharm request for additional information.

The proposed drug product contains Ciprofloxacin HCl 0.3% (a fluoroquinolone antibacterial agent) and is indicated for use in the treatment of bacterial conjunctivitis and corneal ulcers. Ciprofloxacin Hydrochloride, the active ingredient in Ciprofloxacin Ointment, is the same drug substance contained in Ciprofloxacin Ophthalmic Solution which was approved for conjunctivitis and keratitis indications on December 31, 1990 (the monograph on Ciprofloxacin HCl, USP. appears in USP XXII, third supplement, p. 2334).

In this NDA the sponsor is requesting a waiver from the requirement of submission of evidence of *In Vivo* Bioavailability Data under 21 CFR 320.22(b)(2). The sponsor is supporting the waiver request upon the fact that Ciprofloxacin Ophthalmic Ointment is applied topically to the eye in the form of an ointment and this preparation is intended for local therapeutic effect. However, according to the Agency regulations, a waiver for the requirement to submit Human Pharmacokinetics and Bioavailability is not granted to ophthalmic products. The sponsor needs to demonstrate if systemic exposure of the "active drug" after ocular administration is occurring or not.

As mentioned above, the sponsor is requesting a waiver because they did not conduct any systemic absorption study using the proposed to-be-marketed 0.3% Ciprofloxacin

Ophthalmic Ointment. However, the sponsor included in the Human Pharmacokinetic and Bioavailability section of this submission data from two pharmacokinetic studies designed to demonstrate systemic exposure of 0.3% Ciprofloxacin Ophthalmic Solution after ocular administration. Considering that the amount of Ciprofloxacin contained in the ophthalmic solution is the same as the dose to be delivered from the ophthalmic ointment and both formulations have similar potentials for systemic absorption, then, the information from the submitted studies could be used to satisfy the agency's requirement of systemic absorption data for ophthalmic products.

In the first study Protocol C-89-59 (Technical Report 026:39800:1089) titled "**Plasma Concentrations of Ciprofloxacin in Normal Volunteers Following Topical Ocular Administration**", twelve volunteers were dosed in each eye every two hours for two days and every four hours for five additional days with 0.3% Ciprofloxacin Ophthalmic Solution. The results of this study indicate that this drug is absorbed systemically after topical ocular administration of 0.3% Ciprofloxacin Solution. However, Ciprofloxacin exposure is low (peak 4.7 ng/mL). It should be noted that this study was previously filed under NDA 19-992 (July 31, 1990 Amendment, Volume 2.3, Page 5-0007). At that time, the Division of Biopharmaceutics did not conduct a formal review of this study, due to the fact that the reviewing medical officer from the Division of Anti-Infective Drug Products considered that a biopharmaceutic review of this submission was not necessary (see Bio-review dated January 9, 1990 in Attachment I). Therefore, this study (Protocol C-89-59) is being formally reviewed in this submission.

The second study Protocol C-91-03 (Technical Report 034:39800:0791) titled "**Determination Of Plasma Concentrations Of Ciprofloxacin In Normal Volunteers Following Topical Ocular Dosing For Corneal Ulcer Indication**" was conducted in 12 volunteers. The main objective was to determine the concentration-time profiles and systemic exposure of Ciprofloxacin following topical ocular administration of 0.3% Ciprofloxacin Ophthalmic Solution after dosing two drops q. 15 minutes for six hours: two drops q. 30 minutes for the remainder of Day 1: two drops every hour for 24 hours: two drops every four hours for five days. The results of this study indicate that systemic exposure to Ciprofloxacin is occurring, however, this exposure is low, with the majority of concentrations between 1 and 3 ng/mL (peak concentration was 4.3 ng/mL).

II. RECOMMENDATION:

The Division of Biopharmaceutics has reviewed NDA 20-369 which was filed on May 21, 1993. It should be noted that all clinical batches were manufactured in Process Development site and no production batches were used in the clinical trials. Therefore, Biopharm feels that an *in vitro* study(s) (i.e., liberation-penetration or some other test) is needed to evaluate that the pilot and production batches are equivalent.

It is necessary to point out that the sponsor did not conduct any systemic absorption study using the proposed to-be-marketed 0.3% Ciprofloxacin Ophthalmic Ointment. However, the sponsor included in the Human Pharmacokinetic and Bioavailability section of this submission data from two pharmacokinetic studies designed to demonstrate systemic exposure of 0.3% Ciprofloxacin Ophthalmic Solution after ocular administration. Considering that the amount of Ciprofloxacin contained in the ophthalmic solution is the same as the dose to be delivered from the ophthalmic ointment and both formulations have similar potentials for systemic absorption, then, in this specific case, the information from the submitted studies could be used to satisfy the agency's requirement of systemic absorption data for the 0.3% Ciprofloxacin Ophthalmic Ointment.

Also, it is necessary to mention that Ciprofloxacin Hydrochloride is commercially available for oral administration in four strengths; 250, 500, 750, and 1000 mg tablets (i.e., Cipro®). Published data (PDR:46 Edition, 1992) show that after single oral administration of 250 mg of this drug, maximum serum concentrations are 1.2 mcg/mL. These levels are approximately 280 times higher than the peak levels seen in studies No. C-91-03 and C-89-59 for 0.3% Ciprofloxacin Ophthalmic Solution. Therefore, the Division of Biopharmaceutics feels that this submission is acceptable, provided the sponsor submits the requested additional *in vitro* information.

For the proposed package insert for Ciloxan™, it is acceptable, provided the changes that are proposed are incorporated into the Clinical Pharmacology section of the package insert.

Please convey the Recommendation as appropriate, Comment No. 7 and Labeling Comments (page 15) to the sponsor.

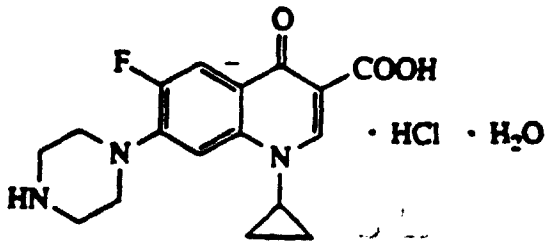
NOTE: Attachment I to V are being retained in the Division of Biopharmaceutics and may be obtained under request.

TABLE OF CONTENTS Page No.

III. BACKGROUND

Since 1980, a number of new 4-quinolone antibiotics with increased *in vitro* potency and broader spectrum antibacterial activity have been synthesized. These fluorinated quinolones are similar in structure to nalidixic acid. The fluorine atom in the Ciprofloxacin molecule enhances antibacterial activity against gram-positive bacteria, the piperazino group increases its effectiveness against gram-negative organisms, and the cyclopropyl group increases the overall potency of the drug. Ciprofloxacin appears to be one of the most potent fluoroquinolones with respect to its ability to inhibit DNA gyrase in bacteria without harming the DNA gyrase in human cells. Published references indicate that Ciprofloxacin has the most effective *in vitro* antibacterial activity against most bacterial species of all the newer fluoroquinolones marketed to date.

Ciprofloxacin HCl



Mw: 385.82

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

IV. DRUG FORMULATION

Ciloxan™ is supplied as a sterile ophthalmic ointment: 3.5 g ophthalmic ointment tube Each gram of Ciloxan Ophthalmic Ointment contains: Active: Ciprofloxacin HCl 3.5 mg equivalent to 3 mg base. Inactive: Mineral Oil, White Petrolatum. The composition of the product proposed for marketing is presented in Table 1. The composition of the formulation and lot No. used in the clinical studies are included in Attachment I.

TABLE 1

Composition of Product Proposed for Marketing

Constituents	mg/g	% w/w	Function	Ref. to Standards
Ciprofloxacin Hydrochloride Monohydrate, Micronized	3.5	0.35(*)	active ingredient	USP XXII
Mineral Oil	20.0	2.0	ointment base constituent	USP XXII
White Petrolatum	to 1.0 g (976.5 mg)	to 100 (97.65)	ointment base constituent	USP XXII

(*)0.35% w/w ciprofloxacin hydrochloride USP (monohydrate) is equivalent to 0.30% w/w ciprofloxacin base (anhydrous) or 0.333% w/w of ciprofloxacin hydrochloride (anhydrous).

V. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY DATA

STUDY PROTOCOL No. C-89-59

TITLE: "Plasma Concentrations of Ciprofloxacin in Normal Volunteers Following Topical Ocular Administration"

OBJECTIVE:

To determine the steady-state plasma concentrations of Ciprofloxacin in normal volunteers following topical ocular application of a 0.3% solution dosed every two hours while awake for two days, then every four hours while awake for five days.

INVESTIGATORS: Philip R. Mayer, Ph.D.
Dan Jasheway, B.S.
Claudia Knowles

STUDY CENTER: Alcon Laboratories, Inc.
Pharmacokinetics/Drug Metabolism

DESIGN:

This Phase-I, open-label, in-house study evaluated concentrations of Ciprofloxacin in blood plasma from 12 healthy volunteers (5 males; age 31-51 years and 7 females; age 28-37 years) following topical ocular application of two drops of 0.3% Ciprofloxacin solution in both eyes every two hours while awake for two days (6:00, 8:00, and 10:00 a.m. and 12:00, 2:00, 4:00, 6:00, 8:00, and 10:00 p.m.) followed by two drops 0.3% Ciprofloxacin solution every four hours while awake for five days (study days 3-7; 6:00 and 10:00 a.m. and 2:00, 6:00, and 10:00 p.m.). A flow chart outlining the study activities at each visit is given in Table 2.

BLOOD SAMPLES:

Blood samples were obtained from each of the twelve subjects at the following times on Study Days 2-7: 5:30 a.m. and 1:30, 3:00, 9:30, 10:30, and 11:00 p.m.

ASSAY VALIDATION:

ed

RESULTS:

All volunteers completed the study. Ciprofloxacin plasma concentrations following topical ocular administration of 0.3% Ciprofloxacin Ophthalmic Solution are presented in Table 3. An estimated plasma concentration-time profile using mean data from study Day 2 is given in Figure 1. Ciprofloxacin plasma concentrations ranged

Plasma concentrations were at their lowest in the morning before dosing began and rose throughout the day as the doses and plasma concentrations accumulated. These limited concentration-time data suggest that Ciprofloxacin concentrations approach steady-state at the end of dosing day, which is to be expected given the four hour plasma elimination half-life in normal individuals.

CONCLUSION:

These results demonstrate that Ciprofloxacin is absorbed systemically following topical administration of 0.3% Ciprofloxacin solution. However, Ciprofloxacin plasma concentrations following a routine ophthalmic treatment regimen were low with the majority of the levels in the range.

TABLE 2

PROTOCOL C-89-59

STUDY PLAN

	Prestudy Screening	Day 1	Day 2	Day 3-6	Day 7	Post Study
Demographics	X					
Medical History	X					
Blood Pressure	X					X
Pulse Rate	X					X
SMA 24	X					X
CBC	X					X
Urinalysis	X					X
Hepatitis B	X					X
HIV	X					X
Pregnancy Test*	X					
Ocular Exam	X					X
Informed Consent	X					
Blood Drawn	X		5:30 am and 1:30, 3:00, 9:30, 10:30 and 11:00 pm		5:30 am and 1:30, 3:00, 9:30, 10:30 and 11:00 pm	
Drops Instilled		6:00, 8:00, 10:00 am, and 12:00, 2:00, 4:00, 6:00, 8:00 10:00 pm	6:00, 8:00, 10:00 am, and 12:00, 2:00, 4:00, 6:00, 8:00 10:00 pm	6:00, 10:00 am and 2:00, 6:00, 10:00 pm	6:00, 10:00 am and 2:00, 6:00, 10:00 pm	

*Female patients only

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

STUDY PROTOCOL No. C-91-03

TITLE: "Determination Of Plasma Concentrations Of Ciprofloxacin In Normal Volunteers Following Topical Ocular Dosing For Corneal Ulcer Indication"

OBJECTIVE:

To determine the steady-state plasma concentrations of Ciprofloxacin in normal volunteers following topical ocular administration of Ciprofloxacin Ophthalmic Solution 0.3% according to the corneal ulcer dosing regimen.

INVESTIGATOR:

STUDY CENTER:

DESIGN:

This Phase-I, open-label study evaluating concentrations of Ciprofloxacin in blood plasma from 12 normal volunteers (8 males; age 20-30 years and 4 females; age 33-60 years) following topical ocular application of Ciloxan (Ciprofloxacin Ophthalmic Solution 0.3%; lot 1ANX). Ciloxan was dosed by placing 2 drops in each subject's right eye every 15 minutes for 6 hours, every 30 minutes for 18 hours, every hour for 24 hours, then every 4 hours for 5 days for a total of 107 doses. All 12 patients were evaluated for Ciprofloxacin concentrations in blood plasma and for safety. A flow chart outlining the study activities at each visit is given in Table 4.

BLOOD SAMPLES:

Blood samples were obtained from each of the twelve subjects to determine the concentration of Ciprofloxacin in plasma. Samples were obtained pre-dose and at 6, 6.5, 22.5, 23.5, 46.5, 47.5, 142.5, and 143.5 hours following the initial medication.

ASSAY VALIDATION:

TABLE 4

Study Flow Chart

	Prestudy Screening	Day 1 Day 1	Day 2 Day 2	Day 3 Day 3	Day 7 Day 7	Post-study
Informed Consent	X					
Medical History	X					
Demographics	X					
Ocular Exam	X					X
Blood Pressure	X					X
Pulse Rate	X					X
SMA 24	X					X
CBC	X					X
Urinalysis	X					X
Pregnancy Test*	X					X
Hepatitis B	X					
HIV	X					
Blood Drawn	X	10:00 p.m.• 4:00 p.m. 4:30 p.m.	8:30 a.m., 9:30 a.m.	8:30 a.m., 9:30 a.m.	8:30 a.m., 9:30 a.m.	
2 Drops Instilled (Right Eye Only)		q 15 min-6 hr; q 30 min-18 hr	q 1 hr around clock	q 4 hr around clock	Last dose at 9:00 a.m.	

*Female patients only
•Prior to initiation of dosing

RESULTS:

All volunteers completed the study. Eleven of the twelve volunteers received 107 doses, and one received 106 doses. Ciprofloxacin plasma concentrations following topical ocular administration of 0.3% Ciprofloxacin Ophthalmic Solution are presented in Table 5.

Topical ocular Ciprofloxacin was absorbed systemically as demonstrated by the concentrations in blood plasma which ranged with the majority of the levels in the range. Ciprofloxacin plasma concentrations were at their highest following the frequent Day 1 dosing. Day 7 concentrations dropped, as the number of daily doses was reduced, to the point of being entirely non-quantifiable Even with the rigorous corneal ulcer dosing regimen, plasma concentrations were very low, approximately 1-3 ng/mL, with some concentrations below sensitivity.

Ciprofloxacin Ophthalmic Solution 0.3% was evaluated for safety in normal subjects. Adverse events related to Ciprofloxacin therapy were generally mild and resolved without treatment. No serious events were observed during the course of the study, and no subject was discontinued from the study due to an adverse event.

CONCLUSION:

The results of this clinical study demonstrate that Ciprofloxacin Ophthalmic Solution 0.3% is absorbed systemically. Following a routine ophthalmic treatment regimen, Ciprofloxacin levels in plasma were low with the majority of the levels in the range.

VI. OVERALL COMMENTS

1. In response to a Biopharm request for additional information, the sponsor submitted on January 12, 1994, an Admendment to NDA 20-369. This document contains the following information:

A. Copy of technical report 026-39800-1089 submitted to NDA 190992 on January 31, 1990 (Vol 2.3 p 50007).

B. Composition of final formulation to be marketed.

C. Composition of investigational formulation including lot No's used in safety and efficacy clinical trials.

D. Manufacturing site of clinical lots including batch size (specify if production lots).

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WAS
DETERMINED
NOT
TO BE
RELEASABLE

2. The information submitted to support the validation of the analytical method used for the determination of Ciprofloxacin in plasma samples is appropriate.

3. Protocols C-89-59 and C-91-03 included both males and female volunteers. The results of these two studies suggest that there are not gender differences in the systemic absorption of Ciprofloxacin. However, the number of subjects is very low for a definite conclusion.

4. It should be noted that Ciprofloxacin Hydrochloride is commercially available for oral administration in four strengths; 250, 500, 750, and 1000 mg film-coated tablets (i.e., Cipro®). Published data (PDR:46 Edition, 1992) show that after single oral administration of 250 mg of this drug, maximum serum concentrations are 1.2 mcg/mL. These levels are approximately 280 times higher than the peak levels seen in studies No. C-91-03 and C-8959 for 0.3% Ciprofloxacin Ophthalmic Solution. The significant difference in plasma levels obtained following oral versus topical ophthalmic dosing indicates a wide safety margin for topical Ciprofloxacin Ophthalmic Solution.

5. It is necessary to point out that the sponsor did not conduct any systemic absorption study using the proposed to-be-marketed 0.3% Ciprofloxacin Ophthalmic Ointment. However, the sponsor included in the Human Pharmacokinetic and Bioavailability section of this submission data from two pharmacokinetic studies designed to demonstrate systemic exposure of 0.3% Ciprofloxacin Ophthalmic Solution after ocular administration. Considering that the amount of Ciprofloxacin contained in the ophthalmic solution is the same as the dose to be delivered from the ophthalmic ointment and both formulations have similar potentials for systemic absorption, then, the information from the submitted studies could be used to satisfy the agency's requirement of systemic absorption data for ophthalmic products.

6. It is necessary to point out that on-face, the proposed to-be-marketed formulation included in the original NDA appears to be different to the formulation used in the clinical studies. Therefore, on February 18, 1994, Biopharm called the sponsor to verify the formula constituents, active ingredient, and ref. to standards (USP XXII Vs British Pharmacopoeia 1993). In this telecon, the sponsor stated that the to-be-marketed formulation for 0.3% Ciprofloxacin Ophthalmic Ointment and the formulation used in the clinical studies are the same formulation. On February 18, the sponsor faxed a table including the composition for the proposed-to-be marketed formulation (see both formulations in Attachment II).

7. All clinical batches were manufactured in Process Development site no production batches were used in the clinical trials. Therefore, it is recommended that an *in vitro* study(s) (i.e., liberation-penetration or some other test) be conducted to evaluate that the pilot batches manufactured in Process Development and the production batches are equivalent.

8. In conclusion, if the medical reviewer of HFD-520 does not have specific issues regarding the safety or efficacy of this drug, then the Division of Biopharmaceutics considers that i) the systemic levels (<0.5 ng/mL) reached after the ocular administration of 0.3% Ciprofloxacin Ophthalmic Solution are not of concern, and ii) the information included in studies C-89-59 and C-91-03 is adequate and it can be used for NDA 20-369 to support the Agency's requirement of systemic data for ophthalmic products. Therefore, NDA 20-369 is acceptable, provided the sponsor submits the additional *in vitro* information requested above (Comment No. 6).

VII. PROPOSED PACKAGE INSERT

The Proposed Package Insert for Ciloxan™ Ophthalmic Ointment is included in Attachment IV.

LABELING COMMENTS:

1. It is recommended to indicate that 12 healthy volunteers (8 males and 4 females) were used in Study C-91-03.

2. Due to the fact that systemic exposure to Ciprofloxacin is occurring, it is recommended to include information regarding the disposition of Ciprofloxacin or cross refer to the *Pharmacokinetics and Metabolism* part of the Clinical Pharmacology section of the package insert of Cipro® Tablets (Ciprofloxacin HCl).

Angelica Dorantes, Ph.D.
Pharmacokinetic Evaluation Branch

RD Initialed by Frank Pelsor, Pharm.D. January 31, 1994

FD Initialed by Frank Pelsor, Pharm.D. 3/1/94

Biopharm Day; (2/7/94) Ludden, Malinowski, Fleischer, Pelsor, Dorantes
cc: NDA 20-369, HFD-520, HFD-340 (Viswanathan), HFD-426 (Fleischer, Pelsor, Dorantes), Drug, Chron, and HFD-19 (FOI)

EXCLUSIVITY SUMMARY for NDA # 20-369 SUPPL # NA

Trade Name Ciloxan Generic Name ciprofloxacin HCl opnthalmic ointment

Applicant Name Alcon Laboratories HFD- 550

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

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

   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?

three years

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

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

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name _____

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

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

YES /___/ NO /✓/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /✓/ NO /___/

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

NDA# 19-992 Ciloxan Solution

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 /___/ NA

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

NDA# _____ NA

NDA# _____ _____

NDA# _____ _____

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

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

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

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

YES /✓/ NO /___/

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

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

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

   YES /✓/ NO /___/

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

   _____

   _____

   YES /___/ NO /___/

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

YES /___/ NO /✓/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /✓/

If yes, explain: _____

_____

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

_____

_____

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

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

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

Investigation #1 88-24 YES /___/ NO /✓/

Investigation #2 #3 88-94 93-58 YES /___/ NO /✓/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /✓/

Investigation #2 #3 YES /___/ NO /✓/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

IND # _____ YES /✓/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /✓/ NO /___/ Explain: _____

43 ✓ _____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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

YES /___/ NO /✓/

If yes, explain: _____

_____

_____ 3/29/98

Signature Date

Title: Deputy Div Director

_____ _____

Signature of Division Director Date

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

Item 14.

Certification

Pursuant to 306(k)(1) of the Federal Food, Drug and Cosmetic Act (21U.S.C. 335a(k)(1). Alcon Laboratories, inc. and Alcon (Puerto Rico) Inc. certifies that, to the best of its knowledge and belief, did not and will not, use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under section 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and an efficacy supplements)

NDA/PLA # **NDA 20-369** Applicant: **Alcon Laboratories**
Supplement #
Therapeutic Class **3S**
Circle one: - SE1 SE2 SE3 SE4 SE5 SE6
Action: (AP) AE NA
HFD-550
Trade (generic) name/dosage form: Ciloxan (ciprofloxacin hydrochloride ophthalmic ointment) 0.3%
Applicant Indication(s) previously approved: N/A

Pediatric labeling of approved indication(s) is adequate ✓ inadequate____

Indication in this application: for the treatment of bacterial conjunctivitis caused by susceptible strains of [redacted] designated microorganisms.
(For supplements, answer the following questions in relation to the proposed indication.)

__X__ 1. **PEDIATRIC LABELING IS ADEQUATE**. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

_____ 2. **PEDIATRIC STUDIES ARE NEEDED**. There is potential for use in children, and further information is required to permit adequate labeling for this use.

_____ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

_____ b. The applicant has committed to doing such studies as will be required.
____ (1) Studies are ongoing,
____ (2) Protocols were submitted and approved.
____ (3) Protocols were submitted and are under review.
____ (4) If no protocol has been submitted, explain the status on the back of this form.

____ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 3. **PEDIATRIC STUDIES ARE NOT NEEDED**. The drug/biologic product has little potential for use in children. Explain why pediatric studies are not needed.:

____ 4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Project Manager March 25, 1998
Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Original [redacted] NDA 20-369
HFD-550/DIV File
NDA/PLA Action Package
HFD-510 G.Troendle (plus, for CDER APs and AEs, copy of action letter and labeling)
NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
5/95

NDA 20-369

May 17, 1994

Joanne B. Marriott
Associate Director, Regulatory Affairs
Alcon Laboratories, Inc.
Post Office Box 6600
Fort Worth, Texas 76115

Dear Ms. Marriott:

Please refer to your new drug application submitted on May 21, 1993, under section 505(b) of the Federal Food, Drug and Cosmetic Act for Ciloxan (ciprofloxacin hydrochloride ophthalmic ointment) 0.3%.

We acknowledge receipt of your amendments and correspondence dated June 23, July 28 and 30, August 20 and 31, October 4, November 5 and 11, December 15 and 21, 1993; and January 5, 12, and 20, 1994.

We have completed our review of this application, as amended, and find that the information presented is inadequate and the application is not approvable. The deficiencies are as follows:

We are reserving comment on the proposed labeling until the application is otherwise approvable.

Also, please be advised that we cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the drug product.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, should you so desire, you may request an informal conference with members of the Division of Topical Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting is to be requested at least 15 days in advance. Should you wish this conference, please call Mrs. Regina Joyce, Consumer Safety Officer, at (301) 443-0335.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other actions under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all deficiencies. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely,

Jonathan K. Wilkin, M.D. 5/12/94
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-369
HFD-540
HFD-80
HFC-130/JAllen
HFD-500
HFD-735
HFD-540/DivDir/JWilkin
HFD-540/SMO/Chambers
HFD-540/MO/Carreras
HFD-520/Micro/Dionne
HFD-540/Pharm/Buko
HFD-520/Chem/Shetty
HFD-340/BioPharm/Dorantes
HFD-540/CSO/Joyce
Init. by RCook 4/4/94; SAlam 3/31/94; ASheldon 4/12/94; TDeCamp 4/11/94 & WAChambers revised 4/18/94

Concurrence Only:
HFD-540/SChem/DeCamp
HFD-540/SMicro/Sheldon
HFD-520/SPharm/Alam
HFD-540/ASCSO/Cook

NOT APPROVABLE

APPEARS THIS WAY
ON ORIGINAL