CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-803

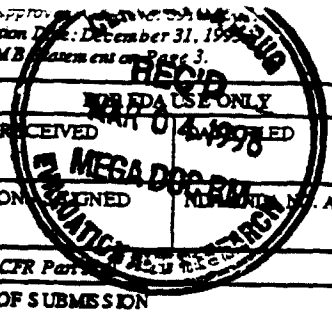
ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

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. 0910-0338
Expiration Date: December 31, 1998
See OMB Statement on Page 3.



FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NUMBER ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 3...)*

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmos Corporation	March 3, 1998
ADDRESS *(Number, Street, City, State and ZIP Code)*	**TELEPHONE NO.** *(Include Area Code)*
33 Wood Ave, South Suite 466 Iselin, NJ 08830	732 603 3526
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 20-803

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Loteprednol etabonate	Alrex

CODE NAME *(If any)*	CHEMICAL NAME
Loteprednol etabonate 0.2% Loteprednol etabonate allergy Core 353	See package insert

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS (S)
Sterile Suspension	Ophthalmic	0.2%

PROPOSED INDICATIONS FOR USE

For the treatment of the signs and symptoms of seasonal allergic conjunctivitis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

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

TYPE SUBMISSION *(Check one)*

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

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

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

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

ORIGINAL

BAUSCH & LOMB
Healthcare and Optics Worldwide

NC
NEW CORRESP

February 6, 1997

Joanne Holmes
Project Manager
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: DESK COPIES
NDA 20-803
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Ms. Holmes:

As requested, enclosed are 10 desk copies of Volume 1.1 and one desk copy of the environmental assessment for the recently submitted NDA 20-803. Also enclosed is a computer diskette containing the package insert in both Word and Word Perfect and two sets of four computer diskettes containing the requested information for each of the four clinical studies submitted in the NDA.

Please let Anna Wysowskyj know if you have any comments or questions about these enclosures. She can be reached by telephone at 813/975-7775 or by fax at 813/975-7757.

Best Regards,

Christine Simmons, Pharm.D
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

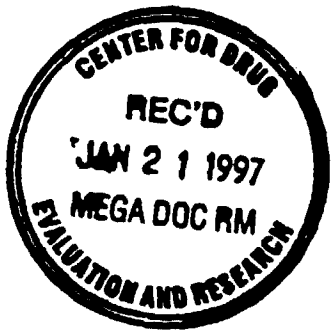
DATE

CSO INITIALS

ORIGINAL

2 Innovation Drive
Alachua, FL 32615
TEL 904-462-1210
904-462-5401

PHARMOS



NEW CORRESPONDENCE

January 10, 1997

Joanne Holmes
FDA, Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products
HFD 550
9201 Corporate Blvd.
Rockville, MD

RE: NDA 20-803

Dear Ms. Holmes:

This letter provides confirmation that, the following personnel listed below at Bausch & Lomb Pharmaceuticals are authorized by Pharmos to contact the FDA on all prior and future issues concerning the above referenced NDA.

Christine Simmons, Director, Regulatory Affairs
Cal Bowman, Vice President, Regulatory Affairs
Ellen Strahlman, M.D., Director of Corporate Medical Affairs

The purpose of this authorization is to facilitate the interchange of data and regulatory information on this program between B & L Pharmaceuticals and the FDA, without the necessity of referencing Pharmos each time.

If you have any questions, please do not hesitate to contact me at 904-462-1210 (phone) or 904-462-5401 (fax).

Sincerely,

G. Riesenfeld

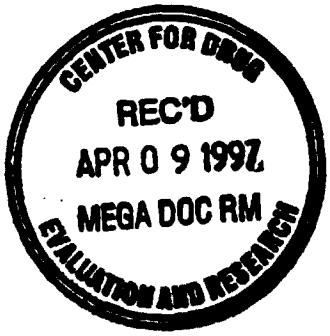
Gad Riesenfeld, Ph.D.
Executive Vice President
Chief Operating Officer

GR/amm

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE



Holmes
550

NDA 20-803

FEB 12 1997

Pharmos Corporation
Attention: C. Christine Simmons, Pharm. D.
Director, Regulatory Affairs
2 Innovation Drive
Alachua, FL 32615

Dear Dr. Simmons:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Therapeutic Classification: Standard

Date of Application: January 31, 1997

Date of Receipt: February 3, 1997

Our Reference Number: 20-803

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 4, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

Lissante C. LoBianco
Acting Supervisor Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-803
HFD-550/Div. Files
HFD-550/Clin Rev/Holmes
HFD-550/SPMS/LoBianco
DISTRICT OFFICE

Drafted by: jh/February 10, 1997/20803.ack

ACKNOWLEDGEMENT (AC)

Pharmaceutical Division
Tampa FL 33637
Fax 813 975 7770

ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

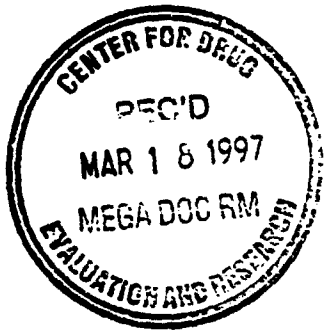
BAUSCH & LOMB
Healthcare and Optics Worldwide

B2

ORIG AMENDMENT

March 17, 1997

Wiley Chambers, MD
Acting Director
Division of Ani-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850



Re: **Amendment to Sections 2, 3, 8, and 10 of NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Dr. Chambers:

As requested by Joanne Holmes, Clinical Reviewer, Pharmos Corporation amends NDA 20-803 with the following:

NDA Section 2:

Disclosure Statement - All safety data from all sources available to the sponsor, U.S. and non-U.S., are included in the application. Loteprednol etabonate is not marketed in any country in any dosage form, so there are no relevant data on marketed product.

Safety Cut-Off Date - The cut-off date for reporting of data from clinical trials is March 1996.

NDA Section 3:

CMC Section in Electronic Format - All portions of the CMC section which are currently available in electronic format are provided on the enclosed diskette. A hard copy of the contents of the diskette is also provided *(Attachment 1)*

In addition, the sponsor amends the application by adding the following statement to the Stability Commitment:

Expiration Dating - Following approval of this NDA, the expiration date of the drug product may be extended based on real time data meeting the requirements of the stability protocols included in NDA Section 3.2.9.3.

NDA Sections 8 and 10:

The case report forms for studies 143 and 144 have been annotated to include the coresponding SAS codes as they appear on the diskettes sent to you on February 6, 1997.

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna B Wysowskyj for

Chris Simmons, PharmD
Director Regulatory Affairs

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

ORIGINAL

BAUSCH & LOMB
Healthcare and Optics Worldwide

April 15, 1997

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850

BC
ORIG AMENDMENT

Re: **Amendment to Section 3 of NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Dr. Chambers:

As requested by Joanne Holmes, Clinical Reviewer, Pharmos Corporation amends Section 3 of NDA 20-803 with additional CMC information regarding the following:

Sampling
In-Process Testing
Filling Operation
Particulates in Packaging Components

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna Wysowskyj

Christine Simmons, PharmD
Director Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

ORIGINAL

V

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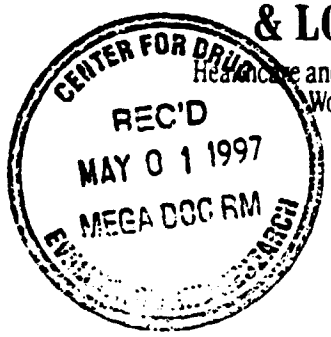


NC
NEW CORRESP

April 30, 1997

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850

Re: **NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Amendment to Pending Application: Trade Names

Dear Dr. Chambers:

Pharmos Corporation amends NDA 20-803 to include two proposed trade names for loteprednol etabonate ophthalmic suspension, 0.2% (see attachment). The original application did not include trade name information for this product.

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna B. Wysowskyj for

Christine Simmons, PharmD
Director Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

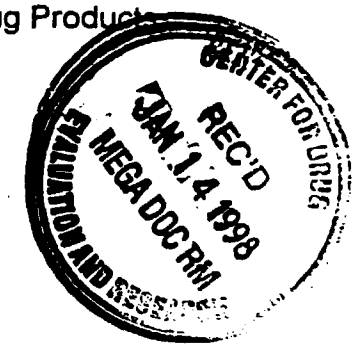
BAUSCH & LOMB
Healthcare and Optics Worldwide

January 13, 1998

ORIGINAL

A2
ORIG AMENDMENT

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Product
HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



RE: **NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
NDA Amendment

Dear Dr. Chambers:

We wish to amend NDA 20-803 by incorporating by reference the amendments submitted to NDA 20-583 on December 10, 1997 and December 11, 1997.

If you have any questions regarding this letter, please contact me at 813/975-7775.

Best Regards,

Christine Simmons

Christine Simmons, Pharm.D
Vice President, Regulatory Affairs

Pharmaceutical Division 8500 Hidden River Parkway, Tampa FL 33637 813 975 7700 Fax 813 975 7770

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Healthcare and Optics Worldwide

January 14, 1998

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

RE: NDA 20-583
Loteprednol Etabonate Ophthalmic Suspension, 0.5%
NDA Amendment

NDA 20-803
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
NDA Amendment

Dear Dr. Chambers:

We wish to amend NDA 20-583 (loteprednol etabonate ophthalmic suspension, 0.5%) and NDA 20-803 (loteprednol etabonate ophthalmic suspension, 0.2%) with the attached information which was faxed to you on January 9, 1998. The faxed information responded to five CMC questions which were faxed by FDA to Bausch & Lomb on January 8, 1998. A copy of the fax containing the five CMC questions is also provided for your reference. All volume and page number references refer to the December 10, 1997 NDA amendment.

If you have any questions regarding this letter, please contact me at 813/975-7775.

Best Regards,

Christine Simmons

Christine Simmons, Pharm.D
Vice President, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-803

JAN 16 1998

Bausch & Lomb
Attention: Christine Simmons, Pharm.D.
Vice President, Regulatory Affairs
8500 Hidden River Parkway
Tampa, Florida 33637

Dear Dr. Simmons:

We acknowledge receipt on January 14, 1998, of your January 13, 1998, amendment to your new drug application for Alrex® (loteprednol etabonate ophthalmic suspension), 0.2%.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is May 3, 1998.

If you have any questions, please contact Lissante C. LoBianco, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

WAC 1/16/98

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
[redacted] NDA 20-803
HFD-550/Div. Files
HFD-550/LoBianco/Chambers/Fenselau 1/16/98
DISTRICT OFFICE
Drafted by: lobianco/January 16, 1998/
saved as n:\lissante\b&l\20803ex.wpd
HFD 105
REVIEW EXTENSION

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

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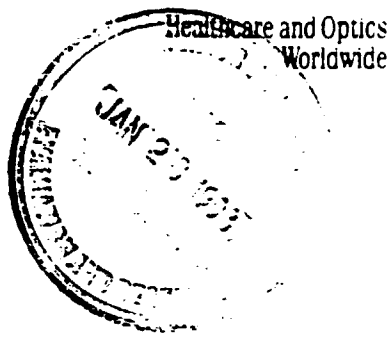
ORIGINAL



January 16, 1998

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850

Re: **NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Microbiology

Dear Dr. Chambers:

PHARMOS Corporation amends NDA 20-803 with the attached information regarding the sterility test method for loteprednol etabonate ophthalmic suspension, 0.2%.

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna Wysowskyj

Anna Wysowskyj
Sr. Manager Regulatory Affairs
Bausch & Lomb Pharmaceuticals, Inc.

BAUSCH
& LOMB
Healthcare and Optics
Worldwide

DUPLICATE

February 26, 1998

BL

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

RE: NDA 20-803
Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%
Revised Draft Labeling

Dear Dr. Chambers:

Enclosed are four copies of revised draft labeling for Alrex™. This labeling incorporates changes to the following sections of the labeling:

Clinical Pharmacology
Contraindications
Warnings
Carcinogenesis, mutagenesis, impairment of fertility
Pregnancy

If you have any questions regarding this submission, please call me at (813) 975-7727.

Best Regards,

Anna B. Wysocky for

Christine Simmons, PharmD
Vice President, Regulatory Affairs, Bausch & Lomb Pharmaceuticals, Inc.
Authorized Agent for PHARMOS Corporation

Tampa FL 33637 Fax 813 975 7770

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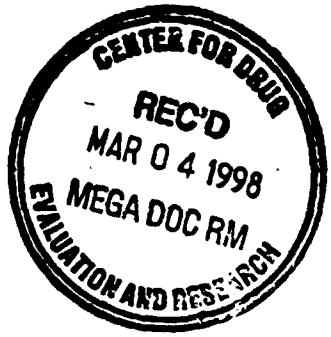
Healthcare and Optics Worldwide

BL

ORIG AMENDMENT

DUPLICATE



March 3, 1998

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

RE: NDA 20-803
Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%
Draft Labeling Change

Dear Dr. Chambers:

We would like to amend NDA 20-803 with a change to the last paragraph of the Adverse Reactions section of the draft labeling submitted on February 26, 1998. A description of the revision is attached.

If you have any questions regarding this submission, please call me at (813) 975-7727.

Best Regards,

Anna B. Wyposky

Christine Simmons, PharmD
Vice President, Regulatory Affairs, Bausch & Lomb Pharmaceuticals, Inc.
Authorized Agent for PHARMOS Corporation

Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

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March 6, 1998

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

RE: **NDA 20-803**
Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%
Revised Draft Labeling

Dear Dr. Chambers:

Enclosed are four copies of revised draft labeling for Alrex™. This labeling incorporates the changes described in the fax we received from you today.

If you have any questions regarding this submission, please call me at (813) 975-7727.

Best Regards,

Anne B. Wypinski for

Christine Simmons, PharmD
Vice President, Regulatory Affairs, Bausch & Lomb Pharmaceuticals, Inc.
Authorized Agent for PHARMOS Corporation

6800 Hidden River Parkway
Tampa FL 33637
813 975 7700
Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

March 9, 1998

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

Re: Amendment
NDA 20-803
Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)
Revision to Package Insert

Dear Dr. Chambers:

Enclosed is a revised page 3 of 5 of the Alrex package insert sent to you on March 6, 1998. The only changes made to the 3-6-98 package insert are corrections of the multiples of the maximum clinical dose identified in the Carcinogenesis and Pregnancy sections of the insert. The corrections reflect the 0.2% loteprednol etabonate concentration of Alrex.

If you have any questions about this information, I can be reached at 813/975-7775.

Best regards,

Christine Simmons

Christine Simmons, Pharm.D
Vice President, Regulatory Affairs

HFD 6-13-97

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Corporate Blvd., Room N461,
Phone #: 827-2391

From: Division of Anti-inflammatory, Analgesic (HFD - 550)
Attention: Allan Fenselau Phone: 827-2502 Date: June 13, 1997

Subject: Request for Assessment of a Trademark for a Proposed Drug Product
NDA#: 20-803, Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Trademark: Currently used: NONE
Proposed: **Alrex™**
Altrin™

Company Name: Pharmos Corporation, 2 Innovation Dr., Alachua, FL 32615

Established name: Loteprednol Etabonate Ophthalmic Suspension, 0.2%
(including dosage form)

Other trademarks by the same firm for companion products: Lotemax™

Indications for Use: Treatment of seasonal allergic conjunctivitis

Initial comments from the submitter (concerns, observations, etc.): None

Chemist Reviewer's Note:

a. Pharmos Corporation filed a request dated 4/30/97 for approval of the above proposed tradenames.

b. The drug product is related to Lotemax™ (loteprednol etabonate, 0.5%, ophthalmic suspension) for ocular inflammation (NDA# 20-583).

Please comment.

Consult #832 (HFD-550)

ALTRIN
ALREX — loteprednol etabonate ophthalmic suspension.

The Committee noted one look-alike/sound-alike conflict with the proposed proprietary name ALTRIN: ALTACE. Although ALTACE is an anti-hypertensive agent in a different dosage form, names with identical first syllables have a high potential for confusion since the last part of the name will trail off unrecognizably in handwritten prescriptions. There were no misleading aspects found with the name.

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name ALREX.

Overall, the Committee found the name ALTRIN unacceptable and the name ALREX acceptable.

8/18/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

NICHOLAS BODOR, Ph.D., D.Sc.

6219 S.W. 93rd Avenue
Gainesville, Florida 32608
Telephone: (904) 377-2988
FAX: (904) 373-7629

February 13, 1995

To Whom It May Concern,

I certify that U.S. Patent No. 4,996,335, "Soft Steroids Having Anti-inflammatory Activity," issued on February 26, 1991, covers loteprednol etabonate and its use as an ocular anti-inflammatory agent.

As the Inventor and Assignee of this patent I further certify that Pharmos Corporation is the sole legitimate licensee of this product in the U.S. for ophthalmic indication.

Yours sincerely,

Nicholas Bodor

NB/jeb

APPEARS THIS WAY
ON ORIGINAL

SECTION 13 PATENT INFORMATION

Information is supplied for two patents as follows:

1.	
Patent Number 4,996,335	
Date Patent Will Expire:	February 26, 2008
Type of Patent:	Composition of matter patent which covers compounds that are used for topical and other localized inflammations, including ophthalmic, involving acute and chronic allergic and inflammatory conditions.
Name of Patent Owner:	Nicholas Bodor

APPEARS THIS WAY
ON ORIGINAL

2.	
Patent Number 5,540,930	
Date Patent Will Expire:	October 25, 2013
Type of Patent:	A composition for ophthalmic or otolaryngological anti-inflammatory use comprising a corticosteroid, a nonionic polymer, a nonionic surface active agent in an amount sufficient to retain the corticosteroid in suspension, and a nonionic tonicity agent.
Name of Patent Owner:	Pharmos Corporation
The undersigned declares that Patent Number 5,540,930 covers the formulation of loteprednol etabonate. This product is the subject of this application for which approval is being sought.	

Authorized Signature: _____

Pharmos Corporation

By: Bausch & Lomb Pharmaceuticals, Inc., as Agent for Pharmos as provided for by 21 CFR 314.53(c)(4)

By: Name: C. Christine Simmons, Pharm.D
Title: Director, Regulatory Affairs

3. **Claimed Exclusivity**

Pursuant to 21 CFR 314.108(b)(4), Pharmos claims five years marketing exclusivity for the product covered by this original new drug application.

New Clinical Investigations: Pharmos certifies that each of the four clinical investigations (LE 141, LE 143, LE 144, LE 145) included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a). These studies have not formed the basis of substantial evidence of effectiveness for a previously approved new drug application.

Essential to Approval: There are no published studies or publicly available reports of clinical investigations known to Pharmos through a literature search that are relevant to the conditions for which Pharmos is seeking approval and were not sponsored by Pharmos. Pharmos certifies that it has thoroughly searched the scientific literature and, to the best of Pharmos' knowledge, the list is complete and accurate and, in Pharmos' opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Pharmos is seeking approval without reference to the new clinical investigations in this application.

Conducted or Sponsored By: Pharmos was the sponsor identified on the Form FDA-1571s submitted to IND 32,432 for the four new clinical investigations submitted in this new drug application. Copies of the Form-1571s are provided.

EXCLUSIVITY SUMMARY for NDA # 20-803 SUPPL # _____

Trade Name Alrex Generic Name loteprednol etabonate ophthalmic suspension 0.2%

Applicant Name Pharmos HFD-550

Approval Date 3/9/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

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

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

YES /✓/ NO /___/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

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

5 years

IF YOU HAVE ANSWERED "NO" TO <u>ALL</u> 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?

YES /[redacted]/ NO /✓/ WAC

If yes, NDA # [redacted] Drug Name [redacted]

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

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

YES /___/ NO /✓/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /✓/ NO /___/

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

NDA # 20-583 _____

NDA # 20-841 _____

NDA # _____ _____

2. Combination product.

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

YES /___/ NO /✓/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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

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

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

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

YES /✓/ NO /___/

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

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

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /✓/ NO /___/

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

_____

_____

(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:

Investigation #1, Study # 141

Investigation #2, Study # 143

Investigation #3, Study # 144

84 145

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

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

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /✓/

Investigation #4 ✓

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /✓/

#4 No ✓

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1, Study # 141

Investigation #2, Study # 143

Investigation #3, Study # 144

Investigation #4, Study # 145

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, 3

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

Investigation #2, 4

IND # YES /✓/ NO /___/ Explain: _____

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

Investigation #1

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

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

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

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

_____ 3/9/98

Signature Date

Title: ✓

Deputy Director

_____ _____

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

NDA 20-583
Loteprednol Etabonate 0.5% Ophthalmic Suspension

Debarment Statement

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Pharmos Corporation, certifies that, to the best of its knowledge and belief, the applicant 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 subsections 306(a) or (b) of the Act.

4. **Debarment Certification**

Pursuant to Section 306(k)(1) of the Federal, Food, Drug and Cosmetic Act, Pharmos Corporation certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity in connection with this application, the services of persons listed pursuant to Section 306(e) as debarred under subsections 306(a) or (b) of the Act.

5. **GLP Certification Statement**

All nonclinical pharmacology/toxicology studies were conducted in compliance with Good Laboratory Practice Regulations as set forth in the U.S. Code of Federal Regulations, Title 21, Part 58 as indicated on the following pages of NDA 20-583:

Study	Title	NDA	Page
P-5604	28-Day Oral (Gavage) Toxicity Study in the Rat	20-583	07 005
P 5604	7-Day Ocular Dose Rangefinding	20-583	07 189
P-5604	28-Day Ocular Toxicity Study in the Rabbit	20-583	07 232
96G-2460	Primary Ocular Irritation - FHSA	20-803	12 004

6. **GCP Certification Statement**

All clinical studies referred to or included in this NDA were conducted in compliance with Institutional Review Board and Informed Consent Regulations as set forth in the U.S. Code of Federal Regulations, Title 21, Part 50 and Part 56 .

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-803 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5

HFD-550 Trade (generic) name/dosage form: Alrex (loteprednol etabonate ophthalmic suspension) 0.2% Action: (AP) AE NA

Applicant Pharmos Therapeutic Class _____

Indication(s) previously approved —

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Allergic conjunctivitis

(For supplements, answer the following questions in relation to the proposed indication.)

___ 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 of discussions 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, on the back of this form, 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.

_____ 3/9/98

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig (NDA)/PLA # 20-803
HFD-550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (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 required at the time of the last action.

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