CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-583

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA 20-583

Pharmos Corporation
Attention: John F. Howes, Ph.D.
Vice President, Clinical and Regulatory Affairs
2 Innovation Drive, Suite A
Alachua, FL 32615

APR 10 1996

Dear Dr. Howes:

Reference is made to your March 29, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% Ophthalmic Suspension.

We acknowledge receipt of your amendments dated April 10 and 13, June 29, July 10 and 13, and October 20, 1995, and March 18, 1996.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical:

1. The studies submitted do not support the proposed indication for the treatment of steroid responsive inflammatory disease. Study 122 fails to demonstrate safety and efficacy of Lotemax in the treatment of uveitis.

Manufacturing Controls:

2.

3.

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Environmental Assessment

5. Information needed to complete an Environmental Assessment of this product is not sufficient and the following information must be submitted:

   a. Information in section 6 of the Environmental Assessment for the French facility used to produce the drug substance. You may provide any one of the following:

      i. the data and information needed to address format items 6a through 6d as detailed in the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*,

      ii. a certification from the French government stating that the facility is in compliance with environmental regulation,

b. Resumes referenced in section 12.

Either delete the reference to the resumes (as they may not be necessary) or provide them to support the statement that they are included.

c. A copy of the environmental assessment for public dissemination.

Of the appendices currently included with the document, only the Materials Safety Data Sheet (MSDSs) and statements of compliance should be included in the Freedom of Information (FOI) releasable environmental assessment. We remind you that sections 7 through 11 and 15 are not normally required for this type of abbreviated environmental assessment.

e. - Information regarding disposal of unused or rejected drug substance. Information similar to that provided for the drug product should be included.

f.

Please note that we cannot approve this application until we are informed that all sites involved in manufacture of the bulk drug and drug product have been found to be in compliance with good manufacturing procedures and are able to perform the production procedures specified in this NDA application.

Deficiencies have been identified in Drug Master Files
Letters have been sent to the DMF holders advising them of these deficiencies. Please note the requirement of 21 CFR 314.420(c) that the DMF holder notify you of changes in their DMF. Until these deficiencies are adequately resolved, the new drug application cannot be approved.

Any resubmission of this application should also include an updated safety report as specified under 21 CFR 314.50(d)(5)(vi)(b).

In addition, although not the basis for the non-approval of this application, the following comments should be addressed in any resubmission of this application:

1. There were a large number of misclassifications in the adverse event tables presented. Similar events were not always coded in the same manner. For example, "Blurry" vision was sometimes coded "Abnormal vision" and sometimes coded as "Blurred vision." Cold was sometimes coded as "Flu Syndrome" and sometimes classified as "Infection." Puffy lids and swollen lids should have been coded together. Unlike events were sometimes coded in the same category. For example: Itching was coded as a "Rash" and increased erythema was classified as a "Rash." A revised classification/coding of the adverse experiences should be submitted.

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We will continue to work with you on the proposed labeling for this product.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products to discuss in detail the deficiencies in this application and what further steps you need to secure approval. The meeting should be requested at least 15 days in advance.

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

Should you have any questions, please contact Joanne Holmes, Project Manager, at 301-827-2090.

Sincerely yours,

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

The following FDA personnel participated in the review of this application:

Sydney Gilman, Ph.D.	Chemistry Reviewer
Joanne Holmes, M.B.A.	Project Manager
Patricia Hughes, Ph.D.	Microbiology Reviewer
David Shriver, Ph.D.	Pharmacology/Toxicology Reviewer
Nancy Silliman, Ph.D.	Statistical Reviewer

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-583
HFD-2/Lumpkin
HFD-105
HFD-550
HFD-80
PHILA DO
HFA-100
HFC-130
HFD-5
HFD-160/Chem/Gilman 4-8-96
HFD-160/SMicro/Cooney
HFD-160/Micro/Hughes 4-8-96
HFD-540/Pharm/Shriver 4-3-96
HFD-550/Pharm/Chen
HFD-550/Chem/Yaciw
HFD-550/ClinRev/Joyce
HFD-550/MO/Chambers
HFD-550/PMS/Holmes
HFD-725/Stat/Silliman 4-4-96
HFD-725/Stat/Harkins 4-3-96
HFD-830/Sheinin
HFD-880/Biopharm/Bashaw 4-4-96

Revised: Chambers/Holmes 4-5-96
Revised: Chambers/Sheinin 4-10-96

NOT APPROVABLE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-583 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade (generic) name/dosage form: Lokmax/loteprednol etabonate ophthalmic Action: (AP) AE NA

Applicant Pharmos Therapeutic Class 15

Indication(s) previously approved None
Pediatric labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application Steroid responsive disease
(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.

X 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.

Susan C Bland, PM — 2/17/98
Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig (NDA)/PLA # 20-583
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 prepared at the time of the last action.

EXCLUSIVITY SUMMARY for NDA # 20-583 **SUPPL #** _____

Trade Name Lotemax **Generic Name** loteprednol etabonate ophthalmic Suspension

Applicant Name Pharmos **HFD-** 550

Approval Date, if known March 9, 1998

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.) _____

   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 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# _____ _____

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 /___/

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.

(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 YES /___/ NO /___/

Investigation #2 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 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: _____
	_____

(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: Regulatory Health Project Manager

_____ 3/9/98

Signature of Division Director Date

Deputy

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

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

Patent Information

Loteprednol Etabonate is a novel chemical entity that is covered in U.S. patent No. 4,996,335 issued on February 26, 1991. The molecule is covered by claim 111 of this patent. The patent is a composition of matter patent which covers the use of the compounds for topical and other localized inflammations including ophthalmic involving acute and chronic allergic and inflammatory conditions.

The Assignee of the patent Nicholas Bodor who has licensed the patent to Pharmos Corporation for its development as an ocular anti-inflammatory agent.

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]

Bodor

[11] **Patent Number: 4,996,335**

[45] **Date of Patent: Feb. 26, 1991**

[54] **SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY**

[75] Inventor: **Nicholas S. Bodor**, 7211 SW. 97th La., Gainesville, Fla. 32608

[73] Assignee: **Nicholas S. Bodor**, Gainesville, Fla.

[21] Appl. No.: **807,034**

[22] Filed: **Dec. 9, 1985**

Related U.S. Application Data

[63] Continuation of Ser. No. 626,535, Jun. 29, 1984, abandoned, which is a continuation of Ser. No. 418,458, Sep. 15, 1982, abandoned, which is a continuation-in-part of Ser. No. 265,785, May 21, 1981, abandoned, which is a continuation-in-part of Ser. No. 168,453, Jul. 10, 1980, abandoned.

[51] Int. Cl.[5] C07J 3/00; A01N 43/50

[52] U.S. Cl. 552/610; 552/611; 552/612

[58] Field of Search 260/397.1; 514/169; 552/610

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,558,675	1/1971	Sarett et al.	260/397.4
3,856,828	12/1974	Phillipps et al.	260/397.1
4,093,721	6/1978	Phillipps et al.	260/397.1
4,242,334	12/1980	Stache et al.	260/397.45
4,263,289	4/1981	Edwards	260/397.1
4,377,575	3/1983	Stache et al.	260/397.45

Primary Examiner—Stanley J. Friedman
Assistant Examiner—Theodore J. Criares
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

The invention provides novel soft steroidal anti-inflammatory agents, pharmaceutical compositions containing said agents, and methods of administering same to mammals in the treatment of inflammation. Preferred compounds of the invention include haloalkyl 17α-alkoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylates and the corresponding $\Delta^{1,4}$ compounds, optionally bearing 6α- and/or 9α-fluorine and 16α- or 16β-methyl substituents. Especially preferred compounds include haloalkyl 17α-alkoxycarbonyloxy-9α-fluoro-11β-hydroxy-16-methylandrosta-1,4-dien-3-one-17β-carboxylates.

113 Claims, No Drawings

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ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL