

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

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**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**

**01 056**

## 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

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ON ORIGINAL

2.

Patent Number 5,540,930

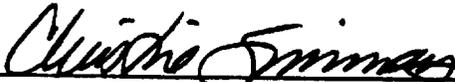
Date Patent Will Expire: October 25, 2013

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 phosphate ophthalmic suspension 0.2%

Applicant Name Pharmos HFD-550

Approval Date 3/7/98

**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 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?

YES /  / NO /  / <sup>WAC</sup>

If yes, NDA # ~~XXXXXXXXXX~~

Drug Name ~~XXXXXXXXXX~~

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:

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- (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: \_\_\_\_\_

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- (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: \_\_\_\_\_

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- (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 / <input checked="" type="checkbox"/> /
Investigation #2	YES /___/	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES /___/	NO / <input checked="" type="checkbox"/> /
Investigation #4		<input checked="" type="checkbox"/>

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 / <input checked="" type="checkbox"/> /
Investigation #2	YES /___/	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES /___/	NO / <input checked="" type="checkbox"/> /
Investigation #4		<input checked="" type="checkbox"/>

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

+ 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 / <u>  </u> / Explain _____	!	NO / <u>  </u> / 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: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_  
 Signature  
 Title:     
*Deputy Director*

  3/9/95    
 Date

\_\_\_\_\_  
 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.**

**APPEARS THIS WAY  
ON ORIGINAL**

**01 058**

**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:

<u>Study</u>	<u>Title</u>	<u>NDA</u>	<u>Page</u>
P-5604	28-Day Oral (Gavage) Toxicity Study in the Rat	20-583	07 005
P 5604	7-Day Ocular Dose Ranging	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 SE6

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

Applicant Pharms 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 form 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.

\_\_\_\_\_  
Signature of Preparer and Title (PM, CSO, MO, other) 3/9/98  
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 filed at the time of the last action.