

FREEDOM OF INFORMATION ACT

NDA 20-803

THE INFORMATION CONTAINED IN

NDA SECTION 3.2.11

CHEMISTRY, MANUFACTURING & CONTROLS

DRUG PRODUCT

ENVIRONMENTAL ASSESSMENT

VOLUME 10

MAY BE MADE AVAILABLE TO THE PUBLIC

LEXICON

THE DRUG SUBSTANCE

LOTEPREDNOL ETABONATE
LE

THE DRUG PRODUCT

LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION
LOTEMAX™ ALLERGY
LOTEMAX™ ANTI-ALLERGY
LEA
LE 0.2%
CORE 353

OTHER LOTEPREDNOL ETABONATE PRODUCT (NDA 20-583)

LOTEPREDNOL ETABONATE 0.5% OPHTHALMIC SUSPENSION
LE
LE 0.5%
LOTEMAX™
CORE 299

MANUFACTURER

BAUSCH & LOMB PHARMACEUTICALS, INC.
BLP
B&L

3.2. Drug Product

3.2.11. Environmental Assessment

Note to the Reviewer:

This Environmental Assessment may be made available to the public under the Freedom of Information Act.

Environmental Assessment Report**Loteprednol Etabonate 0.2% Ophthalmic Suspension**

- 1. Date** December 1996
- 2. Name of Applicant** PHARMOS Corporation
- 3. Address**
2 Innovation Drive
Alachua, Florida 32615
Tel: 904 452-1210
Fax: 904 462-5401

4. Description of the Proposed Action**a. The Proposed Requested Approval**

Pharmos Corporation is submitting a New Drug Application (NDA) for approval of loteprednol etabonate 0.2% ophthalmic suspension (LE 0.2%).

b. Need for the Action

LE 0.2% is a topical product which will be used in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. Annually, an estimated 2.3 million Americans use prescription medications to treat this condition. Loteprednol etabonate (LE) is derived from prednisolone and possesses a potency similar to dexamethasone but causes fewer side effects than other corticosteroids in the treatment of intraocular inflammation. LE is presumed to act at the glucocorticoid (Type II) receptors.

c. Locations Where the Product Will Be Produced

The drug substance will be manufactured by

SIPSY
Route De Beaucouzé - B.P. 79
49242 Avrillé Cedex
France
Tel: 33-41-43-32-11
Fax: 33-41-42-75-55

The drug product will be manufactured by

Bausch & Lomb Pharmaceuticals, Inc.
5800 Hidden River Parkway
Tampa FL 33637
Tel: 813 975-7700
Fax: 813 975-7757

d. Locations Where the Product Will Be Used and Disposed Of

Once approved, LE 0.2% will be used by individuals throughout the United States, primarily on an out-patient basis. Disposal of unused product by the consumer will be through municipal and private household trash collection.

Bausch & Lomb will be responsible for returned and rejected goods. The product will be taken out of any outer packaging which, along with the package insert, will be recycled separately. The plastic containers will be emptied, shredded, rinsed, and recycled. The liquid contents will be collected and disposed of as a non-hazardous substance. (See Item 6 b for additional information on disposal.)

Bausch & Lomb is located in an urban area having a flat terrain and a subtropical climate.

5. Identification of Chemical Substances That Are Subject to the Proposed Action

a. Drug Substance Identification

Common Name: Ioteprednol etabonate

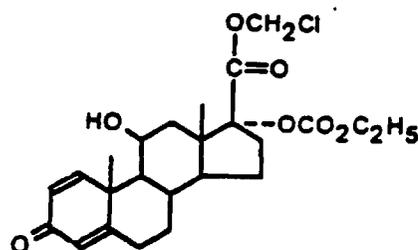
Chemical Names: Androsta-1,4-diene-7-carboxylic acid, 17-
 [(ethoxycarbonyloxy)-11-hydroxy-3-oxo-
 chloromethyl ester, (11 β , 17 α)-
 Chloromethyl 17-ethoxycarbonyloxy-11 β -hydroxy-3-
 oxo-androstra-1,4-diene-17 β -carboxylate

CAS Number: 82034-46-6

Molecular Weight: 466.96

Molecular Formula: C₂₄H₃₁O₇Cl

Structural Formula:



Loteprednol Etabonate

b. Drug Substance Physical Description

Appearance: White crystalline powder

Melting Point: 232 \pm 2°C

Vapor Pressure: Not determined

pH: Not applicable; Loteprednol Etabonate has no ionizable groups

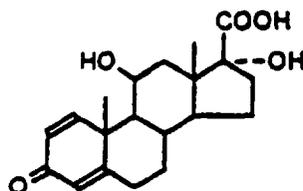
Solubility: DMSO: 34.05% DMF, 31.75%
 Ethanol: 0.8365% Propylene Glycol: 0.2241%
 Water: 0.0008%, or 8 μ g L⁻¹

Partitioning: 3.04 (log K_{acetonitrile/water}) (Ref.: Alberth *et al.*, 1991)

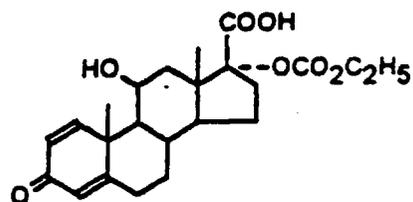
Additives: None. (Benzalkonium chloride is present as a preservative.)

c. Drug Substance Impurities

As supplied, loteprednol etabonate has no significant amounts of impurities ($\leq 2\%$). In the proposed drug product, the chief impurities are Δ_1 cortienic acid etabonate (PJ-91) and Δ_1 cortienic acid (PJ-90) (sum of the two $\leq 0.05\%$ w/v). Both impurities are closely related to LE and may arise from any of the following: synthesis (drug substance), hydrolysis (drug product), or metabolism (in humans).



PJ-90 (Pharmos)



PJ-91 (Pharmos)

d. Excipients

The excipients used in LE 0.2% are common USP/NF pharmaceutical ingredients: glycerin, povidone, tyloxapol, edetate disodium dihydrate, benzalkonium chloride, purified water, and sodium hydroxide or hydrochloric acid (as pH adjusters).

6. Introduction of Substances into the Environment**a. Drug Substance Manufacturing - SIPSY (France)**

Emissions of loteprednol etabonate will be controlled by SIPSY in such a way as to ensure compliance with all local emissions requirements (see appendix). This includes the disposal of unused rejected drug substance.

b. Drug Product Manufacturing - Bausch & Lomb (Tampa FL)

In the production facility, adequate ventilation during raw material handling and product compounding will be provided to maintain dust and vapor levels below the TLV, STEL, and PEL values for the ingredients. Personal protective equipment (e.g., NIOSH-approved respirators, goggles or safety glasses, gloves, and protective clothing) will be used. The minimal amounts of materials emitted into the air will be trapped in HEPA filters. Spills will be collected and containerized for disposal. Total annual solid waste quantities will be less than 2.5 kg, assuming an annual usage rate of 50 kg of loteprednol etabonate drug substance and a 5% loss (waste) rate. Both solid and liquid wastes from the production of LE 0.2% will be disposed of as non-hazardous waste by a licensed facility. Bausch & Lomb currently contracts with following firm for non-hazardous waste disposal:

Ogden Martin
Okahumpka FL
Air Permit A035193817 (Renewal filed 12/96)
Solids Permit S035279397 (Expires 12/18/00)

Waste waters from equipment cleaning, processing residues, and the contents of rejected and returned product will be filtered and neutralized in Bausch & Lomb's waste water processing tanks, then discharged into the City of Tampa POTW (sewer) under

Bausch & Lomb Pharmaceuticals, Inc.
Tampa FL
Industrial Wastewater Discharge Permit 1072 (Expires 5/31/98)

A copy of this permit is provided in the appendix.

Packaging wastes generated during production or from return goods are segregated as plastics or paper and may be recycled at any of several local private recycling facilities, including

BFI Recycling Services
Clearwater FL

There are no regulated air, water, or solid waste emission or substance parameters for the production of LE 0.2%. No OSHA-regulated components are present in the formulation.

The production and related handling of LE 0.2% at the Bausch & Lomb facility will not pose a threat to any endangered species nor to any registered National Historic Preservation Sites.

c. Consumer Use

As is true of any drug, a portion of LE 0.2% is excreted by the user. Nearly all of the excreted material is in the form of metabolites.

The following equation is used to calculate the maximum expected environmental concentration (MEEC) or sewer concentration of loteprednol etabonate entering the front end of a wastewater treatment plant

$$\text{MEEC (ppm)} = A \times B \times C \times D \times E \times F$$

A = kg/year production

B = year/365 days

C = day person/567.81liters (daily sewer usage)

D = $1/246 \times 10^6$ people (U.S. population)

E = 10^6 mg/kg (conversion factor)

F = 1 million

For LE 0.2%, with an anticipated associated maximum annual production of 50 kg loteprednol etabonate, the MEEC may be calculated as follows:

$$\text{MEEC} = 1.96 \times 10^{-8} \times 50 \text{ kg (maximum annual production)}$$

$$= 9.8 \times 10^{-7} \text{ mg/L (ppm)}$$

This value is the MEEC of loteprednol etabonate entering a WWTP; it does not reflect any depletion mechanisms such as biodegradation, hydrolysis or photosynthesis. The molecular structure indicates that LE should be susceptible to hydrolysis and biodegradation. Human metabolism will also affect the above relationship by depleting concentrations of LE with subsequent conversion to two polar metabolites PJ-90 and PJ-91 (see Item 5c).

7. Fate of Emitted Substances

This item not required under 21 CFR § 25.31 a (b).

8. Environmental Effects of Released Substances

This item not required under 21 CFR § 25.31 a (b).

9. Use of Resources and Energy

This item not required under 21 CFR § 25.31 a (b).

10. Mitigation Measures

This item not required under 21 CFR § 25.31 a (b).

11. Alternatives to the Proposed Action

This item not required under 21 CFR § 25.31 a (b).

12. List of Preparers

Anna Wysowskyj, MBA
Manager Regulatory Affairs
Bausch & Lomb Pharmaceutical, Inc.

Danny O. Helton, PhD
Senior Director Product Development
PHARMOS Corporation

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Date 12/19/96

Signature of Responsible Official Danny O. Helton

Title Senior Director Product Development

14. References

None

15. Appendix

MSDS - Loteprednol Etabonate Drug Substance

MSDS - Loteprednol Etabonate 0.2% Ophthalmic Suspension

Compliance Statement - SIPSY (France)

Certificate of Compliance - Ministry of the Environment (Loire Region)

Applicable Regulations - SIPSY (France)

Compliance Statement - Bausch & Lomb Pharmaceuticals, Inc. (Tampa)

Wastewater Discharge Permit 1072 - City of Tampa

Appendix

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION

MATERIAL SAFETY DATA SHEET

Issued:
Revised: 1/06/97

Prepared by: Harold H. Shlevin, Ph.D.
VP - Research & Development

1. PRODUCT AND COMPANY IDENTIFICATION

Product Name: LOTEMAX - Allergy (interim name)
Generic Name: Loteprednol Etabonate
Ophthalmic Suspension, 0.2% (Sterile)
NDC No.: 24208-353-25, 24208-353-05, 24208-353-10

Legal Category: Prescription only medicine, filled in dropper-tipped plastic bottle suitable for dispensing, and overpacked inside a cardboard carton.

Drug Composition: Glucocorticoid

Company: BAUSCH & LOMB PHARMACEUTICALS, INC.
8500 Hidden River Parkway
Tampa, FL 33637 USA

Information: (800) 323-0000 (M-F) 8 a.m. - 5 pm EST
Emergency: (800) 227-1427

2. COMPOSITION/INFORMATION ON INGREDIENTS

Description	CAS#	TLV(mg/m ³)	PEL(mg/m ³)	% Content
Loteprednol Etabonate	82034-46-6	NE	NE	0.2
Glycerin	56-81-5	10	NE	≥1
Povidone	9003-39-8	NE	NE	>1
Purified Water	NA	NE	NE	≥1

Ingredients <1%: Tyloxapol, Edetate Disodium, Benzalkonium Chloride

3. HAZARDS IDENTIFICATION

**BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTE Prednol Etabonate 0.2% Ophthalmic Suspension**

EMERGENCY OVERVIEW

Plastic bottle in cardboard box. Milky white suspension. Toxic by ingestion.

POTENTIAL HEALTH HAZARDS

Carcinogenicity:

(NTP) No (IARC) No (OSHA) No

Eye: May cause irritation, burning sensation on instillation and hypersensitivity (anaphylactic) in some individuals. Studies in animals indicate that topical adrenocoids, when used in large amounts, can be systemically absorbed and can cause fetal abnormalities. Clinical studies indicate that ocular applied loteprednol etabonate (0.5%) does not result in detectable plasma drug levels.

Systemic: Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Systemic toxicity reactions include reversible hypothalamic-pituitary-adrenal axis gland suppression, manifestations of Cushing's syndrome, intercranial hypertension, hyperglycemia and glycosuria in some patients.

Skin: May cause irritation and localized hypersensitivity in some individuals with itching, swelling and diffused redness of the skin.

Ingestion: May cause irritation and hypersensitivity in some individuals. Large doses can induce vomiting, diarrhea, adrenal gland suppression, Cushing's syndrome, water retention, electrolyte imbalance and hyperglycemia.

Inhalation: May cause irritation and hypersensitivity in some individuals.

Chronic Effects: May cause hypersensitivity. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Prolonged ocular use can result in elevation of intraocular pressure, with damage to the optic nerve, defects in visual acuity and fields of vision and/or in posterior subcapsular cataract formation. It may also aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues.

Target Organs: Eyes, skin, digestive tract, kidney and brain.

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTE Prednol Etabonate 0.2% Ophthalmic Suspension

Medical Conditions Aggravated by Long Term Exposure:

- * Anaphylactic cross-reactions may occur for glucocorticoids.
- * Preexisting conjunctival or systemic fungal infections may be aggravated.
- * Appropriate measures should be taken if this occurs.
- * Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and other viral diseases of the cornea and conjunctiva.
- * Tuberculosis of the eye.
- * Fungal diseases of the ocular structures.
- * Hypersensitivity to any of the ingredients of the medication.
- * Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.
- * Acute purulent untreated infection of the eye can be masked or activity enhanced by the presence of corticosteroid medication.

4. FIRST AID MEASURES

Eyes: Rinse immediately with copious amounts of water for at least 20 minutes. Contact a physician.

Skin: Remove all contaminated clothing and wash skin with copious amounts of water for at least 20 minutes. Contact physician if skin becomes irritated.

Ingestion: Wash out mouth. Give plenty of water and bland fluids. Do not give anything to an unconscious person. Contact physician.

Inhalation: Remove person to fresh air, and if breathing stops, use artificial respiration. Contact physician.

Note to Physicians: None

5. FIRE FIGHTING MEASURES

Flammable Properties:

Flash point: NE **Method:** NE

Hazardous Products: Emits toxic fumes.

Extinguishing Media: Dry chemical, carbon dioxide, halon, water spray or fog, and foam on surrounding materials.

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTE Prednol Etabonate 0.2% Ophthalmic Suspension

Fire fighting Instructions: Wear self-contained breathing apparatus and protective clothing. Use water spray to keep fire-exposed containers cool.

6. ACCIDENTAL RELEASE MEASURES

Large/Small spills: Use personal protective equipment. Contain the spill to prevent drainage into sewers, drains or streams. Use absorbent material to solidify the spill. Shovel or scoop up solidified waste. Dispose of material according to Federal, State and Local regulations.

7. HANDLING & STORAGE

Handling: Avoid contact with product and use caution to prevent puncturing containers. No special protective equipment or procedures are required in the clinical or home environment.

Storage: Store product upright in original containers with the cap tightly closed at a controlled room temperature 15°-30°C (59°-86°F). **KEEP THIS AND ALL OTHER DRUGS OUT OF THE REACH OF CHILDREN.**

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls: In the manufacturing plant, provide adequate ventilation for the raw material handling and compounding process which will maintain the dust and vapor levels below the TLV, STEL, and PEL values for the ingredients. Use of suitable respiratory protection equipment is recommended when handling the raw material. Ventilation fans should be explosion proof. Use adequate personal protective equipment, e.g. NIOSH-approved respirators, goggles or safety glasses, gloves and protective clothing. Ensure training in the handling of the chemical materials and use current Material Safety Data Sheets.

Eye Protection: (29 CFR 1910.133) Recommend goggles or chemical safety glasses.

Skin Protection: Thick impermeable gloves and protective clothing.

Respiratory Protection: (29 CFR 1910.134) NIOSH approved respirator recommended for handling raw materials. **Warning:** Do not use air purifying respirators in oxygen depleted environments. No respiratory protection is required in the clinical or home environment.

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION

Other: None

Ventilation: Recommended.

Contaminated Equipment: Wash contaminated clothing separately. Wash equipment with soap and water. Release rinse water into an approved wastewater system or according to Federal, State and Local regulations.

9. PHYSICAL & CHEMICAL PROPERTIES

Appearance & Odor:	Milky white suspension.		
Boiling Point:	NE	Evaporation Rate:	NE
Specific Gravity	1.0	Vapor Density:	NE
Vapor Pressure:	NE	Viscosity:	NE

10. STABILITY & REACTIVITY

Chemical Stability: Stable

Conditions to avoid: Extreme heat or cold.

Incompatibility: This product has the incompatibilities of water e.g. strong acids, bases, alkali metals, alkali hydrides.

Hazardous Decomposition Products: Emits toxic fumes.

Hazardous Polymerization: Should not occur.

11. TOXICOLOGY INFORMATION

Summary of Risks: Toxicological information refers to the raw materials of the product. Concentrations and toxicological effects are substantially reduced in the product. For more detailed information see MSDS on chemical material.

CAS #

82034-46-6 Loteprednol Etabonate

May cause irritation to the eyes, skin and respiratory tract. Can cause hypersensitivity (anaphylactic) in some individuals. Adverse reactions to corticosteroids include suppression of adrenal gland secretion, Cushing's syndrome, water retention, electrolyte imbalance and hyper-glycemia. Studies in animals indicate that topical adrenocorticoids, when used in large amounts, can be

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTEPREDNOL ETABONATE 0.2% X

systemically absorbed and can cause fetal abnormalities. Immune suppression may result from chronic high doses.

56-81-5 Glycerin

May cause irritation to eyes and skin. Repeated or prolonged exposure can cause dermatitis or eye conjunctivitis. Inhalation is not likely due to low evaporation rate, but fumes may cause irritation and defatting of the tissues. Ingestion can cause headache, restlessness, insomnia, dizziness, vomiting, diarrhea and fever. Large doses can cause hemolysis, hemoglobinuria, hyperglycemia, glycosuria, renal failure, convulsions, narcosis and paralysis. Oral-rat LD₅₀ 12,600 mg/kg. Decomposition release corrosive fumes of acrolein. Avoid open flame and extreme heat. Incompatibilities include strong acids, strong oxidizers, metal oxides and metal hydrides.

9003-39-8 Povidone

Acute: prolonged or repeated contact may cause skin or eye irritation. Inhalation may result in respiratory irritation. Ingestion may result in gastric disturbances.
Chronic: Due to presence of a synthetic by product, chronic over-exposure may result in liver or kidney injury.

12. ECOLOGICAL INFORMATION

Chemical Fate Information: Product administered to patients presents a negligible impact on the environment.

13. DISPOSAL CONSIDERATIONS

Dispose of material according to Federal, State, and Local regulations. The method typically used is incineration.

Transportation Data: DOT SHIPPING CLASSIFICATION: WASTE
CONSUMER COMMODITY

EPA Designations: RCRA Hazardous Waste: Not Listed

SARA Title III: Not Listed

14. TRANSPORT INFORMATION

Transportation Data: DOT SHIPPING CLASSIFICATION: CONSUMER
COMMODITY

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTEPREDNOL ETABONATE 0.2% X

15. REGULATORY INFORMATION

EPA Designations: RCRA Hazardous Waste (40 CFR 261.33) Not Listed

FDA Designations: Prescriptions only medication. NDC No. Not available.

OSHA Designations: (29 CFR 1910.1000, Table Z) Not Listed

SARA Title III: Not Listed

16. OTHER INFORMATION

None

The information contained herein is furnished without warranty of any kind. The above information is believed to be correct but does not purport to be all inclusive and should be used only as a guide. Users should make independent determinations of the suitability and completeness of information from all sources to assure proper use and disposal of these materials and the safety and health of employees and customers.

NE - Not Established
< - Less Than
> - Greater Than