ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LOTEMAX™
(Loteprednol Etabonate)
0.5% Ophthalmic Suspension
NDA 20-841

Pharmos Corporation

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS (HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-841

Lotemax™

(Loteprednol Etabonate)

0.5% Ophthalmic Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Lotemax™, PHARMOS Corporation has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(b)(3)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product.

Loteprednol Etabonate is a chemically synthesized drug which is administered as a sterile ophthalmic suspension in treatment of post-operative inflammation following ocular surgery. The drug substance is made at [redacted] and the drug product is manufactured by Bausch & Lomb, Tampa, Florida. The finished drug product will be used mainly by patients in their homes.

Loteprednol Etabonate may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Drug product that expires, or is returned from the field will be separated from the packaging and disposed of as a non-hazardous substance at a licenced facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal

quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

/S/

July 1, 1997
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/S/

7/1/97
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)
Material Safety Data Sheet (drug product)
Compliance Statement
Certificate of Compliance
Applicable Regulations
Compliance Statement - Bausch & Lomb Pharmaceuticals
Wastewater Discharge Permit 1072

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 30, 1997

TO: Those Concerned

FROM: Carl J. Berninger, Ph.D., Environmental Scientist
HFD-357

SUBJECT: Caption Error in Pharmos Environmental Assessment for Lotemax™ (Loteprednol Etabonate Ophthalmic Suspension, 0.5%), NDA 20-841

The Pharmos Environmental Assessment caption, at the top of each page, is incorrect as to the NDA number. The correct NDA number is 20-841.

Environmental Assessment Report
Lotemax™ (loteprednol etabonate 0.5% ophthalmic suspension)
NDA ~~20-681~~ 20-841

Note to the Reviewer:

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

Environmental Assessment Report
Lotemax™ (loteprednol etabonate 0.5% ophthalmic suspension)
NDA 20-~~581~~ 841

1. **Date** March 1997

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

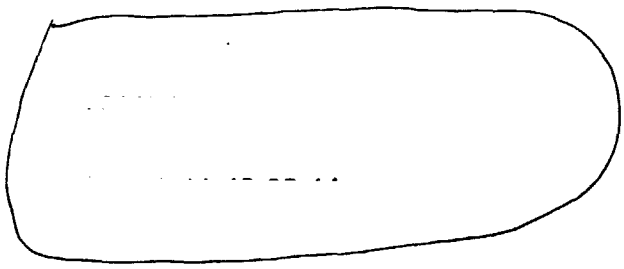
Pharmos Corporation is submitting NDA 20-~~581~~ 841 for the use of loteprednol etabonate 0.5% ophthalmic suspension (LE 0.5%) in the treatment of post-operative inflammation following ocular surgery. This represents a new indication for the LE 0.5% drug product which is the subject of NDA 20-~~585~~ 583.

b. Need for the Action

LE 0.5% is a topical product which, under NDA 20-~~581~~ 841, will be used the treatment of post-operative inflammation following ocular surgery. Annually, an estimated 5.4 million Americans use prescription medications to treat this condition. Loteprednol etabonate (LE) is derived from prednisolone and posseses 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



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 for the post-operative inflammation indication, LE 0.5% will be used by individuals throughout the United States. Use will be 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.)

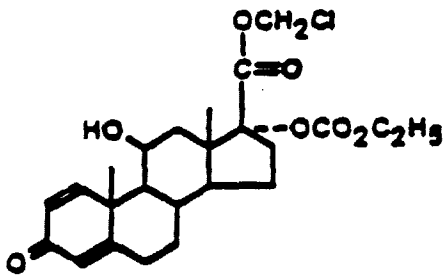
Bausch & Lomb is located in an urban area having a flat terrain and a subtropical climate.

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

a. Drug Substance Identification

Environmental Assessment Report
Lotemax™ (loteprednol etabonate 0.5% ophthalmic suspension)
NDA 20-~~681~~ 841

Common Name:	loteprednol etabonate
Chemical Names:	Chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3–oxoandrosta-1,4-diene-17β-carboxylate
CAS Number:	82034-46-6
Molecular Weight:	466.96
Molecular Formula:	$C_{24}H_{31}O_7Cl$
Structural Formula:	



Loteprednol Etabonate

b. Drug Substance Physical Description

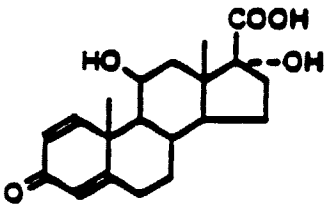
Appearance:	White to off-white powder	
Melting Point:	232 ± 2°C	
Vapor Pressure:	Not determined	
pH:	Not applicable; Loteprednol Etabonate has no ionizable groups	
Solubility:	DMSO:	34.05% DMF, 31.75%
	Ethanol:	0.8365% Propylene Glycol: 0.2241%
	Water:	0.0008%, or 8 μg L^{-1}

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

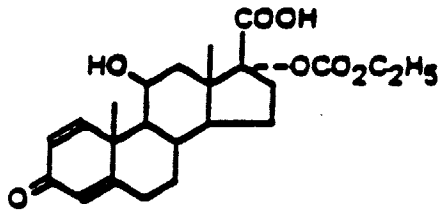
Additives: None. (Benzalkonium chloride is present as a preservative.)

c. Drug Substance Impurities

As supplied, loteprednol etabonate has no significant amounts of impurities (≤ 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 ≤ 0.05% w/v). Both impurities are closely related to LE and may arise from any of the following: [redacted] or metabolism (in humans).



PJ-90 (Pharmos)



PJ-91 (Pharmos)

d. Excipients

The excipients used in LE 0.5% are common USP/NF pharmaceutical ingredients: edetate disodium, glycerin, povidone, purified water, tyloxapol, benzalkonium chloride and sodium hydroxide or hydrochloric acid (as pH adjusters).

6. Introduction of Substances into the Environment

a. Drug Substance Manufacturing [redacted]

Emissions of loteprednol etabonate will controlled by [redacted] 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 wil 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 0.5% 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

Environmental Assessment Report
Lotemax™ (loteprednol etabonate 0.5% ophthalmic suspension)
NDA 20-584 &4 1

There are no regulated air, water, or solid waste emission or substance parameters for the production of LE 0.5%. No OSHA-regulated components are present in the formulation.

The production and related handling of LE 0.5% 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 0.5% 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

MEEC (ppm) = A X B X C X D X E X F

A =
B =
C =
D =
E =
F =

A conservative estimate of A is arrived at by assuming that the entire patient population is treated with following labeled dosing instructions and a is incurred during production.

Drug Product Usage/Yr =

Drug Product Production/Yr =

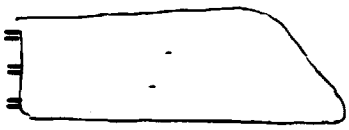
Based on loteprednol etabonate, the maximum annual drug substance requirement would be

Drug Substance Production/Yr =

Drug Substance Loss/Yr =

Thus,

Environmental Assessment Report
Lotemax™ (loteprednol etabonate 0.5% ophthalmic suspension)
NDA 20-~~681~~ 841

MEEC = 

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 3/26/97

Signature of Responsible Official Danny O. Helton

Title Senior Director Product Development

APPEARS THIS WAY
ON ORIGINAL

14. References

None

15. Appendix

MSDS - Loteprednol Etabonate Drug Substance

MSDS - Loteprednol Etabonate 0.5% Ophthalmic Suspension

Compliance Statement [redacted]

Certificate of Compliance - [redacted]

Applicable Regulations [redacted]

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

Wastewater Discharge Permit 1072 - City of Tampa

Appendix

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

CONFIDENTIAL BUSINESS INFORMATION

Material Safety Data Sheet

LOTEPREDNOL ETABONATE
Identity (Trade Name as Used on Label)

Pharmos Corporation
Manufacturer's Name

ND
MSDS Number

2 Innovation Drive
Address

82034-46-6
CAS Number

Alachua, FL 32615

(904) 462-1210
Phone Number for Information

same as above
Emergency Phone Number

Prepared By

NOTE: Blank spaces are not permitted. If any item is not applicable, or no information is available, the space must be marked to indicate that.

SECTION 1 - MATERIAL IDENTIFICATION AND INFORMATION

COMPONENTS - Chemical Name & Common Names (Hazardous Components 1% or greater; Carcinogens 0.1% or Greater)	%	OSHA PEL	ACGIH TLV	OTHER LIMITS RECOMMENDED
Chloromethyl-17α-ethoxycarbonyl-11β-hydroxy-androsta-1,4-diene-3-one-17β-carboxylate	100			
Non-Hazardous Ingredients				
TOTAL	100			

SECTION 2 - PHYSICAL / CHEMICAL CHARACTERISTICS

Boiling Point	ND	Specific Gravity (H2O = 1)	ND
Vapor Pressure (mm Hg and Temperature)	ND	Melting Point	~ 232°C
Vapor Density (Air = 1)	ND	Evaporation Rate (_____ = 1)	ND
Solubility in Water	< 0.1 mg/ml	Water Reactivity	NA

Appearance and Odor: White crystalline powder

SECTION 3 - FIRE AND EXPLOSION HAZARD DATA

Flash Point and Method Used	NA	Autoignition Temperature	NA	Flammability Limits in Air % by Volume	NA	LEL	NA	UEL	NA

Extinguishing Media: NA

Special Fire Fighting Procedures: none required

Unusual Fire and Explosion Hazards: none known

SECTION 4 - REACTIVITY HAZARD DATA

Stability
☐ Stable
☐ Unstable

Conditions to Avoid: none known

Incompatibility (Materials to Avoid): none known

Hazardous Decomposition Products: none known

HAZARDOUS POLYMERIZATION
☐ May Occur
☐ Will not Occur

Conditions To Avoid: none known

SECTION 5 - HEALTH HAZARD DATA

PRIMARY ROUTES OF ENTRY: ☐ Inhalation ☐ Skin Absorption ☐ Ingestion ☐ Not Hazardous

CARCINOGEN LISTED IN: ☐ NTP ☐ IARC Monographs ☐ OSHA ☐ Not Listed

HEALTH HAZARDS
Acute: None are known, but the chemical, physical, and toxicological properties have not been thoroughly investigated

Chronic: None are known, but the chemical, physical, and toxicological properties have not been thoroughly investigated

Signs and Symptoms of Exposure: none known

Medical Conditions Generally Aggravated by Exposure: none known

EMERGENCY FIRST AID PROCEDURES - Seek medical attention for further treatment, observation and support if necessary

Eye Contact: Immediately flush eyes with copious amounts of water for at least 15 minutes.

Skin Contact: Immediately wash skin with soap and copious amounts of water.

Inhalation: Remove to fresh air. If not breathing or breathing is difficult seek medical assistance.

Ingestion: No special procedures known.

SECTION 6 - CONTROL AND PROTECTIVE MEASURES

Respiratory Protection (Specify Type): Avoid contact and inhalation. Do not get in eyes, on skin or clothing.

Protective Gloves: Rubber gloves recommended

Eye Protection: Safety glasses recommended.

VENTILATION TO BE USED
☐ Local Exhaust ☐ Mechanical (General) ☐ Special
☐ Other (Specify) Avoid contact, use with adequate ventilation.

Other Protective Clothing and Equipment: none known

Hygienic Work Practices: Follow above recommendations

SECTION 7 - PRECAUTIONS FOR SAFE HANDLING AND USE / LEAK PROCEDURES

Steps to be Taken if Material is Spilled or Released: Collect spillage. Avoid contact.

Waste Disposal Methods: Observe all federal, state and local laws.

Precautions to be Taken in Handling and Storage: Store in cool, dry place. Keep tightly closed.

Other Precautions and/or Special Hazards: Although none are known, due care should be exercised in it's us

The above information is believed to be correct, but does not purport to be complete and would only be used as a guide. Pharmos Corp. shall not be held liable for any damage resulting from handling or from contact with the above product.

NFPA Rating: Health ___ Flammability ___ Reactivity ___ Special ___ HMIS Rating: Health ___ Flammability ___ Reactivity ___ Personal protection ___

CONFIDENTIAL BUSINESS INFORMATION

BAUSCH & LOMB

Pharmaceutical Division

MATERIAL SAFETY DATA SHEET

Issued: 09/07/94
Revised: NA

Prepared by: [redacted] EHS Chemist **Reviewed by:** [redacted] EHS Specialist

1. PRODUCT AND COMPANY IDENTIFICATION

Product Name: LOTEMAX
Generic Name: Loteprednol Etabonate Ophthalmic Suspension, 0.5% USP (Sterile)
NDC No. Not Available

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

Drug Composition: Glucocorticoid

BAUSCH & LOMB PHARMACEUTICALS, INC.
8500 Hidden River Parkway
Tampa, FL. 33637
Information: (800) 323-0000 (M-F) 8am-5pm EST
Emergency: (800) 227-1427 24 hrs

2. COMPOSITION/INFORMATION ON INGREDIENTS

Description	CAS #	TLV(mg/m^3)	PEL(mg/m^3)	% Content
Loteprednol Etabonate	82034-46-6	NE	NE	[redacted]
Glycerin	56-81-5	10	NE	
Polyvinyl	9002-89-5	NE	NE	
Purified Water	NA	NE	NE	

[redacted]

Povidone, Tyloxapol, Edetate Disodium, Benzalkonium Chloride

3. HAZARDS IDENTIFICATION

****

EMERGENCY OVERVIEW

Plastic bottle in cardboard box. White suspension. Toxic by ingestion.

****

POTENTIAL HEALTH HAZARDS

Carcinogenicity:
(NTP) No (IARC) No (OSHA) No

Eye: May cause irritation, burning sensation on installation 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. 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 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.

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.

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 15^0-30^0 C (59^0- 86^0 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. 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 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.

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: White suspension.

Boiling Point:	NE	Evaporation Rate:	NE
Specific Gravity:	1.0	Vapor Density:	NE
Vapor Pressure:	NE	Viscosity:	NE
Water Solubility:	Complete	Percent Volatile by Volume:	<1

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 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 LD_{50} 12,600 mg/kg. Decomposition releases corrosive fumes of acrolein. Avoid open flame and extreme heat. Incompatibilities include strong acids, strong oxidizers, metal oxides and metal hydrides.

9002-89-5 **Polyvinyl Alcohol**

Dust may cause irritation to eyes and respiratory tract. Inhalation can induce bronchitis or asthma attacks in some individuals. No known dermal effects due to acute exposure. No chronic effects are expected. Oral toxicity is low. Avoid ingestion. Degradation products of stored material are methanol (PEL=260 mg/M^3) and methyl acetate (TLV=200 ppm). Decomposition products are acetaldehyde, crotonaldehyde and acetone. Oral-rat LD_{50} >10 mg/kg. Acetaldehyde: CAS# 75-07-0; TLV=100 ppm; Suspected Carcinogen. Crotonaldyhyde: CAS# 4170-30-3;

PEL=2 ppm; Suspected Carcinogen. Acetone: CAS# 67-64-1; TLV= 750 ppm.

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.

EPA Designations: RCRA Hazardous Waste: Not Listed

SARA Title III: Not Listed

14. TRANSPORT INFORMATION

Transportation Data: DOT SHIPPING CLASSIFICATION; CONSUMER COMMODITY

15. REGULATORY INFORMATION

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

FDA Designations: Prescription only medication. NDC No. 24208

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

APPEARS THIS WAY
ON ORIGINAL

26 SEP. 1994

[redacted]

F - ENVIRONMENTAL IMPACT ANALYSIS

We certify that LOTEPREDNOL ETABONATE manufactured by [redacted] is produced according to the local regulations concerning :

- safety of workers
- safety of installations
- waste disposal
- environmental agency

The plant is regularly inspected by our local representatives to check the compliance with these regulations

GENERAL MANAGER

[redacted]

2 pages
Redacted
confidential
commercial

Pharmaceutical Division | 3500 [illegible] Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

March 26, 1997

Compliance Statement

Bausch & Lomb Pharmaceuticals, Inc. states that is in full compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees, and administrative orders applicable to the production of

Loteprednol Etabonate 0.5% Ophthalmic Suspension
(Post-Operative Inflammation Indication)

at its facilities in Tampa FL as well as all emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of loteprednol etabonate 0.5% ophthalmic suspension (post-operative inflammation indication) at its facilities in Tampa FL.

Eileen Farinacci
Vice-President of Operations

APPEARS THIS WAY
ON ORIGINAL

Industry Name Bausch & Lomb Pharmaceutical Permit No. 1072

Acceptance of Permit

Bausch & Lomb Pharmaceutical accepts the conditions of the permit and
(name of company)

agrees to meet the conditions herein.

Permit period: June 1, 1996 through May 31, 1998

By _____ 6/26/96
(signature) (date)

*Name Anthony Caracciolo

Title Vice-President of Operations

* Must be the owner or an authorized representative of the company.

(Return this signed page to the Industrial Waste Division)

CITY OF TAMPA

Department of Sanitary Sewers

Howard F. Curren
Advanced Wastewater Treatment Plant

Mr. Anthony Caracciolo
Bausch & Lomb Pharmaceutical
8500 Hidden River Parkway
Tampa, FL 33637

June 18, 1996

Re: Issuance of a Wastewater Discharge Permit to Bausch & Lomb Pharmaceutical, by the City of Tampa, Department of Sanitary Sewers.

Dear Mr. Caracciolo:

The enclosed issued permit, No. 1072, governs the wastewater discharge from the facility located at 8500 Hidden River Parkway, Tampa, Florida 33637, into the City of Tampa's wastewater collection system. All discharges from this facility and actions and reports relating thereto shall be in accordance with the terms and conditions of this permit.

The discharge permit is attached to this letter. I am enclosing two copies of the front page of the discharge permit with a block reserved for your signature indicating acceptance of the limitations and conditions specified in this permit. Please sign both copies of the front page of the permit and return one of the signed copies to John M. Daily, City of Tampa, Industrial Waste Division, 2700 Maritime Blvd., Tampa, FL 33605.

If you have any questions about this permit please do not hesitate to contact John M. Daily at 247-3451.

Sincerely,

Ralph L. Metcalf II, P.E.
Director
Department of Sanitary Sewers

RLM:jmd

2700 Maritime Boulevard • Tampa, Florida 33605 • 813/247-3451 • Fax: 813/248-5269

CITY OF TAMPA

DEPARTMENT OF SANITARY SEWERS

INDUSTRIAL WASTEWATER DISCHARGE PERMIT

City of Tampa

Department of Sanitary Sewers

Industrial Wastewater Discharge Permit

Cover Page

Permit No. 1072

In accordance with the provisions of Section 26-122 of the City of Tampa Code:

Company Name Bausch & Lomb Pharmaceutical

Address 8500 Hidden River Parkway

Telephone Number 975-7700

Name of Applicant Anthony Carnecciolo

Is hereby authorized to discharge industrial wastewater from the above identified facility and through the outf identified herein into the City of Tampa sewer system in accordance with the conditions set forth in this per Compliance with this permit does not relieve the permittee of its obligation to comply with any or all applica pretreatment regulations, standards or requirements under local, State, and Federal laws, including any s regulations, standards, requirements, or laws that may become effective during the term of this permit.

Noncompliance with any term or condition of this permit shall constitute a violation of the City of Tampa se use ordinance.

This permit shall become effective on June 1, 1996
and shall expire at midnight on May 31, 1998

If the permittee wishes to continue to discharge after the expiration date of this permit, an application must filed for a renewal permit a minimum of 90 days prior to the expiration date.

6/10/96
Date

Director
Department of Sanitary Sewers