CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-583

ENVIRONMENTAL ASSESSMENT and/or FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LOTEMAX
(Loteprednol Etabonate)
Ophthalmic Suspension (Sterile)
NDA 20-583

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

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(Loteprednol Etabonate)

Ophthalmic Suspension (Sterile)

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 to treat inflammatory or allergic conditions of the eye. The drug substance is made at SIPSY, Avrille', France and the drug product is manufactured by Bausch & Lomb, Tampa, Florida. The finished drug product will be used in hospitals, clinics and 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 the 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 substance and product that fail specification, pass expiration period, or are returned from the field are destroyed by high temperature incineration or by land filling in approved and regulated facilities. 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.

3/4/97
Date

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

3/5/97
Date

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

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)
Preclinical Pharmacology and Toxicity Studies

ENVIRONMENTAL ASSESSMENT REPORT FOI
NDA - 20-583

Item 1. Date: April 1996

Item 2. Name of Applicant: PHARMOS Corporation

Item 3. Address: 2 Innovation Drive
Alachua, Florida 32615
T: 904 462-1210
F: 904 462-5401

Item 4. Description of the Proposed Action:

PHARMOS is submitting an EA for Loteprednol Etabonate (LE); a topical ophthalmic anti-inflammatory corticosteroid. LE qualifies for "abbreviated" EA based on 21 CFR 25.31a(b) which states that for approval of NDAs for human drugs when the drugs are for ophthalmic or topical application only information on Format Item 6 (Introduction of Substances into the Environment) is required while documentation on Format Items 7-11 and 15 are not required. In this report, ~~Items 7-11 and 15~~ NS 3/5/97 ~~containing~~ relevant *in vivo* and *in vitro* information on mammalian species have been included. These studies demonstrate hydrolytic degradation of LE to two polar non-glucocorticoid metabolites in mammalian species. Therefore, following patient use, the actual chemical products entering a sewage treatment plant will be small quantities of metabolites. This information coupled with a low annual production of 100 kilograms (kg) demonstrates that there will be only small quantities of metabolites entering a sewage treatment plant and little to no parent drug substance. This is supported by an MEEC (Maximum Expected Environmental Concentration or sewer concentration reaching front end of a wastewater treatment plant) calculation for LE of 0.002 micrograms per liter (μg/L) (ppb) which considers annual production of 100 kg of parent drug and no metabolism or other abiotic transformation (e.g., photolysis, hydrolysis, biodegradation). Other transformation/degradation mechanisms would further decrease parent drug substance concentrations down to the parts per trillion range. Since metabolism of LE yields two metabolites and little to no parent drug substance, the product actually entering the wastewater treatment plant will be water soluble metabolites in the parts per trillion range. This more realistic scenario as an example for the aquatic compartment, would give a calculated EEC (MEEC-depletion processes) for the metabolites in the low parts per trillion range.

LE is derived from prednisolone and possesses a potency similar to dexamethasone but it causes fewer side effects than other corticosteroids in the treatment of intraocular inflammation. LE is presumed to act at the glucocorticoid (Type II) receptors.

LE will be used by individuals throughout the United States (initially not more than one million people per year) to treat inflammatory or allergic conditions of the eye. It will be used on an outpatient (i.e., home and workplace) or an in-patient (hospital) basis. Production of the "drug substance" is in France, while production of the "drug product" will occur at Bausch & Lomb's Tampa facilities. Returned or rejected goods will be taken out of the packaging. Plastic wrap and paper box (and paper insert) will be recycled separately. The plastic containers will be shredded, rinsed, and recycled. The product will be collected and disposed as a non-hazardous substance by Bausch & Lomb.

Item 5. Identification:

Common Name: Loteprednol Etabonate

Chemical Names:

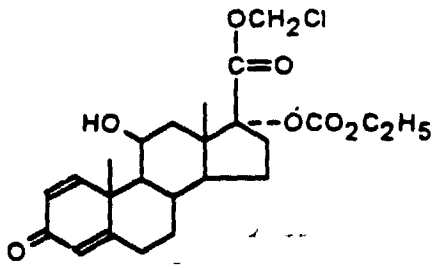
1. Androsta-1,4-diene-17-carboxylic acid, 17-[(ethoxycarbonyl)oxy]-11-hydroxy-3-oxo-, chloromethyl ester, (11β,17α)-
2. Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxy-3-oxo-androstra-1,4-diene-17β-carboxylate

CAS Number: 82034-46-6

Molecular Weight: 466.96

Molecular Formula: $C_{24}H_{31}O_7Cl$

Structural Formula:



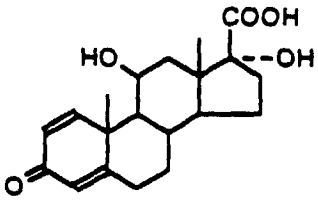
Loteprednol Etabonate

Physical Description:

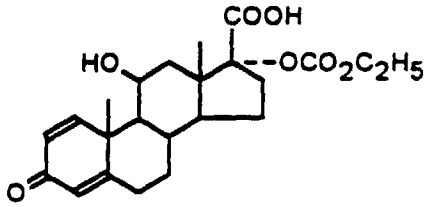
Appearance:	White crystalline powder
Melting Point:	232±2°C
Vapor Pressure:	Not determined.
pH:	Not applicable; Loteprednol Etabonate has no ionizable groups.
Solubility:	DMSO: 34.05%DMF, 31.75%
	Ethanol: 0.8365%Propylene Glycol: 0.2241%
	Water: 0.0008%, or 8 $\mu g\ l^{-1}$
Partitioning:	3.04 (log K _____) (Reference: Alberth *et al.*, 1991)
Additives:	None. (Benzalkonium chloride is present as a preservative.)

Impurities:

As supplied, the drug has no significant amounts of impurities. Nine impurities with a total concentration equal to or less than 2% (≤2%) have been noted in the Drug Substance Final Specification. Upon storage or exposure to high temperatures (but those within the ambient levels of the warm season), Δ_1 cortienic acid etabonate (PJ-91) and Δ_1 cortienic acid (PJ-90), occur as a breakdown product. The Drug Product document will indicate that the sum of PJ-90 + PJ-91 will not exceed 5%. Both Δ_1 cortienic acid etabonate and Δ_1 cortienic acid are components of the synthesis pathway from prednisolone hydrolysis by-products from Drug Product storage, and metabolic products.



PJ-90 (Pharmos)



PJ-91 (Pharmos)

Item 6. Introduction of Substances into the Environment:

The drug substance is produced in France, while the "formulation" product will be processed at Bausch & Lomb's Tampa facilities (8500 Hidden River Parkway, Tampa, Florida 33637).

The ingredients used in the production of the formulation are Loteprednol Etabonate, Glycerin, Povidone, Tyloxapol, Edetate Disodium, Benzalkonium chloride, and purified water. The material safety data sheet

(MSDS) from Bausch & Lomb is included in Appendix 1. In the production facility, adequate ventilation for the raw material handling and compounding process will be provided to maintain the 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.

There are no regulated emission or substance parameters for the formulation. Emissions into the air are nonexistent and there are minimal nonregulated effluents as cleaning residuals. The substances to be disposed of as wastes are the LE product total solid nonregulated wastes, which will be taken away and disposed of by a contractor. Waste levels over a 5-year period are expected to be between 150 and 300 grams of Loteprednol Etabonate per year. The waste quantities were calculated by assuming:

1. The product production level to be 3,000 liters for the first year and 6,000 liters in subsequent years, and
2. A manufacturing loss (waste) rate of 5 percent.

There are no regulated air, water, or solid waste permit limit parameters for the production of the formulation product. No OSHA-regulated ingredients are in the present formulation of LE. A statement of compliance from Bausch & Lomb facilities is provided in Appendix 2, and a compliance statement from Sipsy is provided in Appendix 3.

The amount (concentration) of active LE that may enter the aquatic environment as a result of use and/or disposal [through wastewater collection systems to wastewater treatment plants (WWTPs)] may be estimated. People who use this or any drug product will expel a portion through excretion, which essentially starts the introduction of the drug into environment. Approximately, 74 percent of the United States population uses sewer systems and publicly-owned treatment works, whereas 26 percent use septic systems whose contents (i.e., sludge) are pumped approximately every 2 years and discharged into sewage treatment plants.

The maximum expected environmental concentration (MEEC) or sewer concentration of substance entering the front end of a WWTP may be calculated as follows:

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

A = kg/year production

B = year/365 days

C = day person/567.75 liters (daily sewer usage)

D = 1/246 x 10^6 people (U.S. population)

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

F = 1 million

For LE with an anticipated maximum annual production of 100 kg, the MEEC may be calculated as follows:

MEEC = 1.96 x 10^{-8} x 100 kg (maximum annual production)

= 1.96 x 10^{-6} mg/L (ppm)

= 0.002 μg/L (ppb)

This value is the MEEC of LE entering a WWTP; it does not reflect any depletion mechanisms such as biodegradation, hydrolysis or photolysis. The molecular structure indicates that LE should be susceptible to hydrolysis and biodegradation. Human (patient) 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 7). Most of the drug substance (MEEC) entering WWTP will be the metabolites at concentrations in the parts per trillion range. Furthermore, the MEEC can be estimated as 74 percent of the calculated MEEC value because pumped out sludges from septic systems that are discharged into publicly owned treatment works will not have drug substance sorbed to the sludge.

Item 7. List of Preparers.

This Environmental Assessment for Loteprednol Etabonate was prepared for PHARMOS by Isabel Johnson of KBN Engineering and Applied Sciences, Inc. Gainesville, Florida, and Roy B. Laughlin, Jr., Ph.D. of Toxikon Environmental Sciences, Jupiter, Florida.

Information used to prepare this environmental assessment was provided by Dan Helton, Ph.D., and John Howes, Ph.D., of PHARMOS, Alachua, Florida.

Item 8. 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 preparation of the environmental assessment.

Date April 15, 1996

Signature of responsible official Danny O. Helton

Title Dir. Product Development

Item 9. References

Copies of preclinical pharmacology and toxicity studies, as well as references, are included in Appendices 4 and 5.

The following documents and sources of information are appended:

Appendix 1. Material Safety Data Sheets (Bausch & Lomb's and PHARMOS')

Appendix 2. Bausch & Lomb's Statement of Compliance

Appendix 3. Sipsy's Statement of Compliance

Appendix 4. Integrated summary non-clinical pharmacology and toxicology of Loteprednol Etabonate.

Appendix 5. Alberth, M., W.M Wu, D. Winwood and N. Bodor. 1991. Lipophilicity, solubility and permeability of Loteprednol Etabonate: A novel, soft anti-inflammatory corticosteroid. J. Biopharm. Sci. 2, 115-125.