

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-769**

**ENVIRONMENTAL ASSESSMENT AND/OR FONSI**

ENVIRONMENTAL ASSESSMENT  
AND  
FINDING OF NO SIGNIFICANT IMPACT  
FOR  
LOCOID Lipocream®  
(hydrocortisone butyrate)  
Cream

NDA 20-769

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION HFD-540

**FINDING OF NO SIGNIFICANT IMPACT**

**NDA 20-769**

**LOCOID Lipocream®**

(hydrocortisone butyrate)

**Cream**

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

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 this action 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, Yamanouchi Europe, B.V. has prepared an abbreviated environmental assessment (21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture and use of LOCOID Lipocream® (hydrocortisone butyrate) Cream, 0.1%. The drug is indicated for the treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The point source(s) of manufacture of the drug substance is at \_\_\_\_\_ and the finished product is at Yamanouchi Europe, B.V., Meppel, The Netherlands. The firm has provided a certification of compliance with the environmental regulations of this foreign government.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used 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. Any residues of hydrocortisone butyrate or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

3/22/97

DATE

PREPARED BY

J. S. Hathaway, Ph.D.  
Chemist

Division of New Drug Chemistry III

8/28/97

DATE

DIVISION CONCURRENCE

Wilson H. DeCamp  
Chemistry Team Leader  
HFD-540

DATE

Approved

Phillip G. Vincent, Ph. D.  
Environmental Assessment Officer  
Office of the Center Director  
Center for Drug Evaluation and Research

DATE

Concurred

Associate Director of Chemistry  
Center for Drug Evaluation and Research

Attachments: Environmental Assessment  
Material Safety Data Sheet (drug substance)

cc: Original NDA 20-769  
Division File/HFD-540

FONSI File \_\_\_\_\_/HFD-540

P. Vincent/HFD-102

Docket File \_\_\_\_\_/HFD-540

FOIA Copy HFD-019 (HOLD UNTIL APPROVED)

F/T / /

## ENVIRONMENTAL ASSESSMENT

This Environmental Assessment is being submitted in accordance with 21CFR §25.31a(a). The subject of this NDA is Locoid® Lipocream (hydrocortisone butyrate). The drug product is a topical drug, and thus qualifies as an Infrequent Use drug under 21CFR §25.31a(b)(3).

1. **Date**

November 25, 1996

2. **Name of Applicant**

Yamanouchi Europe, B.V.

3. **Address**

The address of the Applicant is:

Elisabethhof 19  
P.O.Box 108  
2350 EC Leiderdorp  
The Netherlands

Correspondence should be directed to:

Mr. Richard J. D'Agostino  
President  
Inveresk Research (North America) Inc.  
4470 Redwood Highway, Suite 101  
San Rafael, CA 94903

4. **Description of Proposed Action**

a. **Requested Approval**

Yamanouchi Europe, B.V. has submitted an NDA (No. 20-769, September 12, 1996) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Locoid® Lipocream (hydrocortisone butyrate) 0.1% packaged in 15 g and 45 g metal (aluminum) tubes with polyethylene closures. This Environmental Assessment is being submitted in accordance with 21CFR §25.31a(a).

**b. Need for Action**

Locoid® Lipocream 0.1% is a topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The drug product is intended for topical use only.

**c. Production Locations**

The drug substance is manufactured by  
for Yamanouchi on a contract basis.

submitted a Drug Master File for hydrocortisone butyrate (DMF  
A letter  
authorizing Yamanouchi Europe B.V. (formerly Brocades Pharma B.V.) to  
reference this DMF may be found in NDA No. 20-769

All of the manufacturing, packaging and quality control testing of the drug  
product are performed by:

Yamanouchi Europe B.V.  
Hogemaat 2, 7942 JG Meppel  
The Netherlands

Postal Address:  
Postbus 43, 7940 AA Meppel  
The Netherlands  
Telephone: 0522 235300  
Central fax: 0522 258794

**d. Locations of Use**

The end use of the drug product will be primarily patients in their own  
homes. No concentrated use in any particular geographic region is  
anticipated.

**e. Disposal Sites**

Information on the method(s) of disposal of rejected, expired, returned or  
waste drug substance may be found in DMF

Information on the method(s) of disposal of rejected, expired, returned or  
waste drug product follows:

Waste materials from production, samples, returned and rejected materials are packed in standard drums and labeled as pharmaceutical waste. The amounts are weighed. The materials are handed over to \_\_\_\_\_ for final disposal. According to contract with \_\_\_\_\_ the pharmaceutical waste is delivered to \_\_\_\_\_. All pharmaceutical waste material is incinerated by \_\_\_\_\_ at one of the state incineration plants for disposal of chemicals. \_\_\_\_\_ keeps a complete account of the amount of waste pharmaceutical materials accepted from Yamanouchi and delivered to \_\_\_\_\_.

In the home, 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, although minimal quantities of unused drug may be disposed of in the sewer system.

**5. Identification of Chemical Substances that are the Subject of the Proposed Action**

**a. Nomenclature**

**i. Established Name (USAN)**

hydrocortisone butyrate, U.S.P.

**ii. Brand/Proprietary Name**

Locoid Lipocream®

**iii. Chemical Names**

**(1) Chemical Abstracts (CA) Index name**

hydrocortisone-17-butyrate

**(2) Systematic Chemical Name**

(1) pregn-4-ene-3, 20-dione, 11,21-dihydroxy-17-(1-oxobutoxy)-, (11β)-;

(2) cortisol 17-butyrate;

(3) 11β, 17, 21-trihydroxypregn-4-ene-3, 20-dione 17-butyrate

b. **Chemical Abstracts Service (CAS) registration number**

CAS Registry No. [13609-67-1]

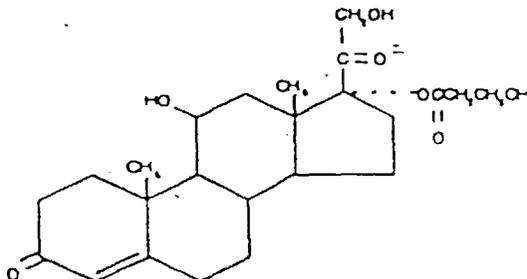
c. **Molecular Formula**

$C_{25}H_{36}O_6$

d. **Molecular Weight**

432.56

e. **Structural Formula**



f. **Physical Description**

White or practically white powder

g. **Additives**

One gram of the drug product contains the drug substance (1 mg) in a vehicle composed of Mineral Oil (████ mg), White Petrolatum (████ mg), Ceteth-20 (████ mg), Cetosteryl alcohol (████ mg), Citric Acid, anhydrous (████ mg), Sodium Citrate, anhydrous (████ mg), Propyl Paraben (preservative) (████ mg), Butyl Paraben (preservative) (████ mg), and Purified Water (████ g).

h. **Impurities**

There are no known impurities in the drug product greater than █%. Hydrocortisone-21-butyrate is a known impurity, but the specification for this impurity in the drug product is █████ mg/g. The drug product also has a specification for total unknown related impurities (measured by peak area relative to the labeled value of the 17-ester) of  $\leq 3.0\%$ .

**6. Introduction of Substances into the Environment**

For information on the drug product, see           DMF

Since the drug product is produced in The Netherlands, a certification from the responsible company official certifying that the           facility is in full compliance with applicable environmental laws and regulations is attached.

**7. Fate of Emitted Substances in the Environment**

This section is not applicable in accordance with 21CFR §25.31a(b)(3).

**8. Environmental Effects of Released Substances**

This section is not applicable in accordance with 21CFR §25.31a(b)(3).

**9. Use of Resources and Energy**

This section is not applicable in accordance with 21CFR §25.31a(b)(3).

**10. Mitigation Measures**

This section is not applicable in accordance with 21CFR §25.31a(b)(3).

**11. Alternatives to the Proposed Action**

This section is not applicable in accordance with 21CFR §25.31a(b)(3).

**12. List of Preparers**

This EA was prepared by Richard J. D'Agostino, President of Inveresk Research (North America) Inc. Mr. D'Agostino has a B.Sc. (Chemistry) and an MBA degree. No other persons, contract laboratories or agencies were consulted or used in the preparation of this EA.

**13. Certification**

The certification required is attached.

**14. References**

There are no references included in this EA.

## 15. Appendices

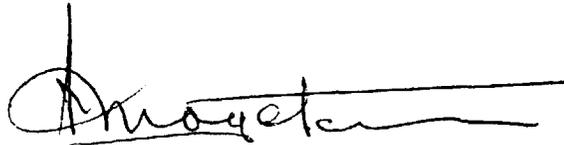
This section is not applicable in accordance with 21CFR §25.31a(b)(3).

STATEMENT

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 EA.

The undersigned official certifies that the EA summary document (page 1-6) contains non-confidential information and knowledges that this information will be made available to the public in accordance with 40 CFR § 1606.6.

Leiderdorp, August 20, 1997



YAMANOUCHI EUROPE B.V.  
A.P. Morgenstern, Ph.D.  
Directory Regulatory Affairs

## CERTIFICATE

RE: Locoid Lipocream USA.

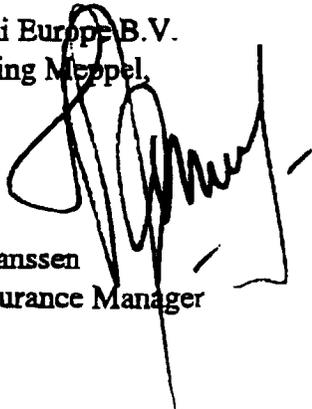
Herewith we declare that

the manufacturing facilities of Yamanouchi Europe B.V. at Meppel, The Netherlands, are in compliance with all local and national environmental laws and are in compliance with all emission requirements set forth in all company permits,

approval and subsequent increase in the production of Locoid Lipocream at the facility is not expected to affect compliance with the current emission requirements or compliance with environmental laws.

Yamanouchi Europe B.V.  
Manufacturing Meppel.

Meppel, The Netherlands,  
August 20, 1997



Dr. H.J.L. Janssen  
Quality Assurance Manager