CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-788

PHARMACOLOGY REVIEW(S)

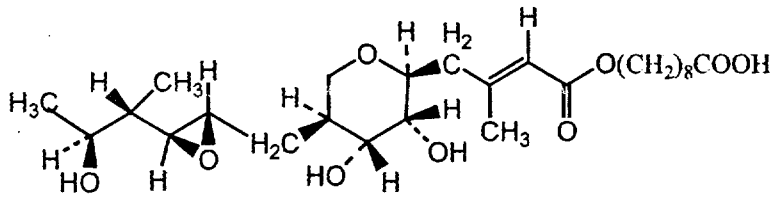
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 50,788
Review number: 1
Sequence number/date/type of submission: 000; 2/7/02; original NDA 505(b)(2) submission
Information to sponsor: No
Sponsor and/or agent: Clay-Park Labs, Inc.; Bronx, NY
Manufacturer for drug substance: [redacted]

Reviewer name: Amy L. Ellis
Division name: Anti-Infective Drug Products
HFD #: 520
Review completion date: 4/17/02

Drug:

Trade name: none
Generic name: Mupirocin Ointment, 2%
Code name: none
Chemical name: [2S-[2α(E),3β,4β,5α[2R*,3R*(1R*,-2R*)]]]-9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxu-5-[[3-(2-hydroxy-1-methylpropyl)oxiranyl]methyl]2H-pyran-2-yl]-2-butenyl]oxy]nonanoic acid
Molecular formula/molecular weight: $C_{26}H_{44}O_9$/500.63
Structure:



Relevant INDs/NDAs/DMFs: [redacted] NDA 50,591 (Bactroban® Ointment); [redacted]

Drug class: Pseudomonic acid antimicrobial

Indication: Impetigo due to *S. aureus* and *S. pyogenes*

Clinical formulation: [redacted], mupirocin [redacted] castor oil, [redacted] oleyl alcohol, [redacted], Softisan 378 (hard fat) [redacted], propylene glycol monostearate (all w/w).

Route of administration: Dermal

Proposed use: Impetigo

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: The pharmacologist has no objection to the approval of this NDA.

B. Recommendation for Nonclinical Studies: None.

C. Recommendations on Labeling: The sponsor is proposing to use exactly the same wording as the Bactroban® label for the *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy* sections. This is acceptable.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: This mupirocin ointment was moderately irritating to rabbit skin when applied for 4 hours daily for 10 days under partial occlusion, in contrast to Bactroban® ointment which was nonirritating under the same conditions.

B. Pharmacologic Activity: Mupirocin is a reversible inhibitor of isoleucyl-tRNA synthetase and causes inhibition of both protein and RNA syntheses in susceptible bacteria.

C. Nonclinical Safety Issues Relevant to Clinical Use: Nothing apparent.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence (TL)- _____

Concurrence (Deputy Div Dir)- _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

PM/Dillon-Parker
MO/Bostwick
Chem/Sloan
Micro/Marsik
Stat/Jiang
Biopharm/Lee

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Mupirocin is a reversible inhibitor of isoleucyl-tRNA synthetase and causes inhibition of both protein and RNA syntheses in susceptible bacteria.

II. SAFETY PHARMACOLOGY:

No safety pharmacology studies were necessary.

III. PHARMACOKINETICS/TOXICOKINETICS:

No nonclinical PK/TK studies were submitted or necessary for this product.

IV. GENERAL TOXICOLOGY:

Only one toxicology study, **Comparative Dermal Irritation in Rabbits** (MB-99-7891.03), was submitted by the sponsor to support this NDA. It was reviewed in [redacted] N-000 by Dr. Terry S. Peters. Mupirocin ointment, 2% or Bactroban® Ointment was applied to the skin of New Zealand White rabbits once daily for 10 days, under partial occlusion, for 4 hours each day. Mupirocin ointment, 2% was a moderate irritant, as manifested by erythema, edema, and flaking of skin. Microscopic evaluation revealed epidermal hyperplasia/hyperkeratosis, inflammatory cell infiltrates in the dermis, and hyperplasia of the sebaceous epithelium. In contrast, Bactroban® was not irritating under the conditions of this study.

V. GENETIC TOXICOLOGY:

The sponsor is relying on data from Glaxo SmithKline's Bactroban® NDA 50,591 to support the current NDA as per 505 (b)(2). According to the label for Bactroban®, mupirocin was negative in the following tests for mutagenesis and/or clastogenesis: unscheduled DNA synthesis in rat primary hepatocytes, sediment analysis for DNA strand breaks, Ames *Salmonella* reversion test, *E. coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

VI. CARCINOGENICITY:

Carcinogenicity studies have not been performed with mupirocin.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

The sponsor is relying on data from Glaxo SmithKline's Bactroban® NDA 50,591 to support the current NDA as per 505 (b)(2). According to the label for Bactroban®, mupirocin did not impair fertility or reproductive performance of rats given subcutaneous doses up to 14 times the recommended human topical dose (based on body surface area). Additionally, no harm

to the fetuses of rats or rabbits was observed when dams received subcutaneous mupirocin doses up to 22 and 43 times the recommended human topical dose (based on body surface area), respectively.

VIII. SPECIAL TOXICOLOGY STUDIES:

None.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

A topical ointment with 2% mupirocin (Bactroban®, Glaxo SmithKline) has been approved previously for impetigo, but the current ointment formulation from Clay-Park differs from the approved formulation. The Division found it acceptable for the sponsor to conduct a rabbit dermal toxicity study with the new formulation to support the clinical tests for irritation and sensitization that were needed for this NDA. The remaining nonclinical data needed to support the NDA and write a label for Clay-Park's product are available in Glaxo SmithKline's NDA 50,591 for Bactroban® and are available under the 505(b)(2) provision. Additionally, Clay-Park stated that they conducted a literature search for mupirocin to find citations for nonclinical studies published after approval of the Bactroban® NDA, but found no new relevant information.

The sponsor also conducted a literature search on the inactive ingredients found in their product. These inactive ingredients do not appear to be of concern when applied topically in the amounts consistent with the application of mupirocin ointment, 2%, when used as directed. Oleyl alcohol is found in other approved topical drug products at concentrations up to 10% and propylene glycol monostearate is present in other creams at [redacted] the same as for this mupirocin ointment. Softisan 378 is not itself found in other approved products, but similar caprylic-capric-stearic acid-based fats are found in many other topicals. Castor oil is very irritating to rabbit skin (and may have contributed to the dermal irritation potential of the current product when it was tested in rabbits), but it is less irritating to the skin of most humans and is frequently used as an emollient in cosmetics. It is present in an approved topical steroid cream at 12.5% and was a primary ingredient [redacted] of the topical aerosol Granulex (a product that was used for debridement).

In the only nonclinical study conducted with Clay-Park's 2% mupirocin ointment, the product was moderately irritating to rabbit skin when applied for 4 hours daily for 10 days under partial occlusion. In contrast, Bactroban® ointment was nonirritating under the same conditions. Clinical testing of the new 2% mupirocin ointment did not indicate that the product caused unacceptable levels of irritation or sensitization in humans.

General Toxicology Issues: None.

Recommendations:

The pharmacologist has no objection to the approval of NDA 50,788 for mupirocin ointment, 2%.

Labeling with basis for findings:

The *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy* sections of the label for this product, mupirocin ointment, 2% will mimic the approved Bactroban® label. This is acceptable and appropriate since the current sponsor is relying on the nonclinical data in the Bactroban® NDA (via 505(b)(2)) that was used to write this label.

X. APPENDIX/ATTACHMENTS:

Addendum to review: None.

Other relevant materials (Studies not reviewed, appended consults, etc.): Nothing to report.

Any compliance issues: No.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Ellis
4/22/02 05:10:58 PM
PHARMACOLOGIST
The pharmacologist has no objection to the approval of this NDA.
Terry- You signed the paper copy of this on 4/19/02.

Terry Peters
4/23/02 06:08:54 AM
PHARMACOLOGIST

Lillian Gavrilovich
4/24/02 02:56:08 PM
MEDICAL OFFICER