CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-746

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

APPENDIX D

ENVIRONMENTAL ASSESSMENT REVIEW

FINDING OF NO SIGNIFICANT IMPACT

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Bactroban® Cream

(Mupirocin Calcium)

2% topical cream

NDA 50-746

FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-746

Bactroban®Cream

Mupirocin Calcium

2% topical cream

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 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 for Bactroban®Cream, SmithKline Beecham Pharmaceuticals has prepared an environmental assessment in accordance with *21 CFR 25.31a(b)(3)*(attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Bactroban®Cream is a naturally occurring antibiotic which is administered as a topical cream containing 2%w/w mupirocin free acid as mupirocin calcium. It will be used in the treatment of secondary infected traumatic skin lesions, such as small lacerations, sutured wounds or abrasions. Mupirocin Calcium the drug substance is manufactured by SmithKline Beecham Worthing facility in the United Kingdom. The drug product Bactroban®Cream will be manufactured by DPT Laboratories, San Antonio, Texas. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

The applicant used the Tier 0 classification and the infrequent use provision for an AEA that limits the information submitted in format items 7, 8, 9, 10, 11, and 15, in accordance with the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (Nov. 1995).

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.

5-27-97
DATE

PREPARED BY
Milton J. Sloan, Ph. D.
Chemist
HFD-520

5-27-97
DATE

DIVISION CONCURRENCE
David B. Katague, Ph. D.
Team Leader
HFD-520

6/3/97
DATE

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachments: Environmental Assessment Review
Non-Confidential EA submitted by applicant

CC: HFD-520/Division File
HFD-357/EA File NDA #50-746
HFD-357/Docket File
HFD-205/FOI COPY

ENVIRONMENTAL ASSESSMENT

REVIEW

FOR

Bactroban® Cream

(Mupirocin Calcium)

2% topical cream

NDA 50-746

FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

1. DATE

17 May 1997

2. NAME OF APPLICANT

SmithKline Beecham Pharmaceuticals

3. ADDRESS

SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

4. DESCRIPTION OF THE PROPOSED ACTION

a. Requested Approval

The applicant is requesting approval for therapeutic use of Bactroban® Cream for treatment of secondary infected traumatic skin lesions, such as small lacerations, sutured wounds or abrasions as additional indications for Bactroban™. An Abbreviated Environmental Assessment for Bactroban Cream Topical refers to the submission of a New Drug Application (NDA# 50-746) and reflects changes related to the additional indication, as compared to the Bactroban Nasal Application (ADA #50-703). Changes to the Environmental Assessment in the original application are found in Sections 1, 4, 6, 7, 8, 9, 10, 11, 12, 14, 15, which correspond to the same sections in the original Confidential Environmental Assessment Information dated September 25, 1992. For details pertaining to the unchanged sections of the Environmental Assessment please refer to Confidential Environmental Assessment report dated September 25, 1992, the Amendment to the Confidential Environmental Assessment Information dated August 30, 1993 (addition of new manufacturing site). Reference is also made to the Non-Confidential version (FOI) of the Environmental Assessment dated January 6, 1994, which was provided in the report as Addendum 1 and a copy attached to this review.

b. Need for Action

The therapeutic indication addressed in this application is for treatment of secondary infected tissue lesions (SITL), such as small lacerations, sutured wounds or abrasions. The active drug substance in Bactroban® Cream is mupirocin free acid derived by submerged fermentation of *Pseudomonas fluorescens*. The commercial product which is the subject of this application is an aqueous cream containing 2.0% w/w mupirocin free acid as mupirocin calcium.

Mupirocin is a naturally occurring antibiotic and is chemically unrelated to other clinically available antibacterial agents [1]. It has a broad range of antibacterial activity against the majority of aerobic Gram-positive bacteria, particularly those most likely to be the cause of primary and secondary skin infections [2,3], including methicillin-resistant *Staphylococcus aureus*. It is also active against certain Gram-negative bacteria.

Mupirocin calcium is a new form of mupirocin in a mineral oil base. The cream formulation has negligible dermal irritancy and has showed no potential for causing sensitization reactions. Additionally, a cream is preferable to an ointment for treatment of certain types of dermatological conditions.

c. Production Locations

For this application, Section **4c** does not differ from Section **4.3** found in the documents described in Section **4a** of this Environmental Assessment report, and no changes are necessary.
Bactroban Bulk Cream drug product and commercial tube filling for 15 g or 30 g aluminum tubes will be prepared at the following facility:

DPT Laboratories
307 East Josephine Street
San Antonio, Texas 78215

Bactroban commercial tube filling for the 0.5 g capacity plastic tube will be prepared at the following facility:

For more details on the filling and packaging operations at these facilities, please reference the Confidential Amendment to Environmental Assessment dated August 30, 1993, and the Non-Confidential version (FOI) of the Environmental Assessment dated January 6, 1994, which is provided as Addendum 1 in this report.

d. Locations of Use

For this application, Section **4d** does not differ from Section **4.4** found in the documents described in Section **4a** of this Environmental Assessment report, and no changes are necessary.

e. Disposal Sites

Disposal of returned, expired and rejected drug substance and proprietary drug substance intermediate will be done in accordance with the environmental certification obtained from each site. All Bactroban™ drug product returned, expired and rejected goods will be collected at and shipped to one of the facilities listed below for disposal by high temperature incineration.

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

SmithKline Beecham Pharmaceuticals in Bristol, Tennessee is permitted by the Tennessee Air Pollution Control Board to operate an infectious waste incinerator under Permit No. 443118. The Air Pollution Control Board regulates air emissions in the state of Tennessee and is part of the Department of Environment and Conservation. The Bristol site was issued a "Conditional Major Source" Operating Permit on June 14, 1996. This permit allows the facility to incinerate returned goods and in-house manufacturing waste. It expires on November 1, 2005.

is licensed by the Florida Department of Environmental Regulation (Orlando, Florida) to destroy hazardous material under permit number A035-193877 (expiration date - October 25, 1996), and under solid waste permit number S035-279397 (expiration date December 18, 2000).

At US hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures. 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.

ACCEPTABLE

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

For descriptions of the active component, Mupirocin Calcium, Section 5 does not differ from Section 5 found in the documents described in Section **4a** of this Environmental Assessment report, and no changes are necessary.

ACCEPTABLE

6. Introduction of the Substances into the Environment

a. Substances Expected to be Emitted

For introduction from production of Bactroban™, Section **6a** does not differ from Section 6.1 found in the documents described in Section **4a** of this Environmental Assessment report with the exception of the exclusion of the SB, Crawley facility as a drug product manufacturing plant for this application.

b. Controls Exercised

Refer to section 6.1 of referenced EA.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Refer to section 6.1 of referenced EA.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Refer to section 6.1 of referenced EA.

e. Expected Introduction Concentrations

Refer to section 6.1 of referenced EA.

i. Expected Introduction Concentration from Use

Bactroban™ (mupirocin calcium cream) Cream, 2% will be produced at DPT Laboratories in San Antonio, Texas. This section reflects a minor name change of the company from previous submissions. The details of existing controls at this manufacturing plant are no longer required based on current Guidance for Industry [4]; however, they are summarized in the documents described in Section 4.1 of this Environmental Assessment report.

ii. Expected Introduction Concentration form Disposal

The returned goods of Bactroban™ will be collected and disposed of as described in Item 4e of this assessment. Based on the controlled and highly efficient thermal destruction of unused Bactroban™, no significant amount of material should be introduced into the environment from disposal.

ACCEPTABLE

7. Fate of Emitted Substances in the Environment

Under the current Guidance For Industry [4], EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed according to the infrequent use provision for drugs of topical application.

ACCEPTABLE

8. Environmental Effects of Released Substances

Under the current Guidance For Industry [4], EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed according to the infrequent use provision for drugs of topical application.

ACCEPTABLE

9. Use of Resources and Energy

Under the current Guidance For Industry [4], EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed according to the infrequent use provision for drugs of topical application.

ACCEPTABLE

10. Mitigation Measures

Under the current Guidance For Industry [4], EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed according to the infrequent use provision for drugs of topical application.

ACCEPTABLE

11. Alternatives to the Proposed Action

Under the current Guidance For Industry [4], EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed according to the infrequent use provision for drugs of topical application.

ACCEPTABLE

12. List of Preparers

12.1 List of Contributors
For this application, Section 12.1 does not differ from the same Section 12.1 found in the documents described in Section **4a** of this Environmental Assessment report, and no changes are necessary.

12.2 Preparers
Staff, Environmental Research Laboratory, SmithKline Beecham
Robert E. Hannah, B.S., Assistant Director
Wilmer Tirado, B.S., M.S., Assistant Director
Renee E. Sims, B.S., Assistant Project Administrator

ACCEPTABLE

13. Certification

James V. McArdle, Ph. D.,Group Director, Analytical Sciences, SmithKline Beecham signed the certification as to the truth, accuracy and completeness of the document on November 1, 1996.

ACCEPTABLE

14. References

[1] Chain, E.B. and Mellows, G. **1977**. The structure of pseudomonic acid A, a novel antibiotic produced by *Pseudomonas fluorescens*. *J Chem Soc.* 1, 294-309.

[2] Basker, M.J., Comber, K.R., Clayton, P.J., Hannan, P.T., Mee, N L-W. Rogers, N.H. Slocombe, B. And Sutherland, R.. **1980**. Ethyl Monate A: Current Chemotherapy and Infectious Disease, Nelson JD and Grassi C 1/471-473. Washington D.C.: *Amer Soc Microbiol.*

[3] White, A.R., Beale, A.S., Boon, R.J., Griffin, K.E., Masters, J.P. and Sutherland, R. 1984. Antibacterial activity of mupirocin. *Excerpta Medica Curr Pract Ser.* 16, 19-34.

[4] Food and Drug Administration, November 1995, *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, Center for Drug Evaluation and Research (CDER), Washington, D.C.

[5] PMA, 1991. Pharmaceutical Manufacturers Association, "*Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA*", v 7, 1991.

ACCEPTABLE

5-27-97
DATE

PREPARED BY
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Review Chemist
ONDC, Chemistry Division III

5-27-97
DATE

DIVISION CONCURRENCE
David B. Katague, Ph. D.
Team Leader
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Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA #: 50-746 (000)

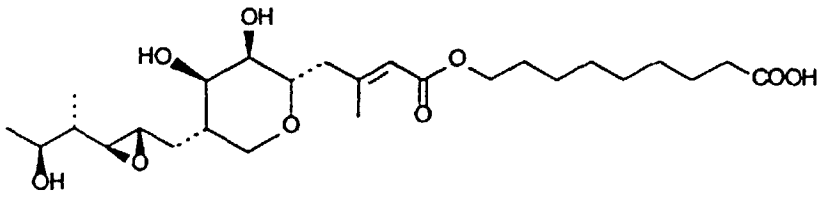
SPONSOR: SmithKline Beecham Pharmaceuticals
Philadelphia, Pennsylvania

AUTHORIZED REPRESENTATIVE: Debra Hackett
(215) 751-4455

DRUG NAMES: Bactroban ® Cream, 2%; mupirocin calcium cream

CATEGORY: Topical antimicrobial cream

STRUCTURAL FORMULA:



RELATED SUBMISSIONS:

NUMBER OF VOLUMES: 6

DATE CDER RECEIVED: 12/12/96

DATE ASSIGNED: 1/8/97

DATE REVIEW STARTED: 1/9/97

DATE 1ST DRAFT COMPLETED: 1/10/97

DATE REVIEW ACCEPTED BY TEAM LEADER: January 14, 1997

REVIEW OBJECTIVES: To determine the nonclinical safety profile of the cream formulation, as well as fact sheets on the two excipients: 2-phenoxyethanol and cetomacrogol

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:

TOXICOLOGY:
Nonclinical studies were conducted with several cream formulations (21073-48, BR 18338, BR 18319, 2172/D). The final formulation selected for marketing is 21073-48.

Formulation 2172/D

1. Primary skin irritation in rabbits with formulation 2172/D:
No GLP compliance statement is included in the report.
Single topical administration was made to intact and abraded, shaved dorsal areas on 6 New Zealand White rabbits. Sites were occluded for 24 hours, and lesions were scored at 1, 24, and 48 hours after removal of the dressing.

Erythema and edema were observed on a single animal at 1 hour, but resolved by 48 hours.

The sponsor concluded that this formulation is a mild irritant to rabbit skin.

2. Primary eye irritation study in rabbits with formulation 2171/D:
A GLP compliance statement is included in this report.
Single ocular application of 0.1 mL of the cream was made to one eye each of 9 female New Zealand White rabbits. In 3 animals, the eye was not rinsed; in two other groups of 3, the eyes were rinsed at 2 and 4 seconds after installation.

Slight redness of the conjunctival membrane was noted in all 9 rabbits, chemosis in 8, and discharge in 7 at the one hour time point. All eyes appeared normal on Day 2.

The sponsor concluded that this formulation is a slight irritant to rabbit eyes.

3. Skin sensitization study in guinea pigs (modified Maguire/split adjuvant method) with 2172/D formulation:
A GLP compliance statement is included in this report.
Clipped backs of 20 Dunkin Hartley guinea pigs were treated with 0.2 mL of 10% sodium dodecyl sulphate in paraffin, and occlusive dressings were applied for 2 hours. Two hours later, the lesions were washed, treated with 0.2 mL of the cream formulation, and reoccluded. Application of the test formula was repeated on Day 2, and Day 3 (after 0.1 mL intradermal injection of complete Freund's adjuvant) and on Day 6. Five additional animals were treated with a positive control substance (DNCB in propylene glycol). Ten negative controls were injected with intradermal Freund's only on Day 3.

On Day 21, 0.2 mL of challenge material was applied to the shaved flanks. Positive controls were challenged with DNCB at 0.2% and 0.02%, all others with mupirocin calcium cream.

No reaction attributable to the test formulation occurred in untreated guinea pigs, or those induced with mupirocin calcium. One treated animal showed erythema, only at the 28 hour time point. This was not considered a typical hypersensitivity reaction.

4. A 10 day topical/toxicity range finding study in male rats with formulation 2172/D:
A GLP compliance statement is included in this report.
Shaved backs of 5 male Sprague-Dawley rats were treated with either vehicle or 40 mg/kg/day of the cream formulation once/day for 10 days.

As no lesions were observed, the 40 mg/kg/day dose was selected as the high dose for the 28 day study.

5. A 10 day topical/toxicity range finding study in rabbits with formulation 2172/D:
A GLP compliance statement is included in this report.
The cream formulation (at 40 mg/kg/day) was applied daily for 10 days to 2 New Zealand White rabbits/sex and vehicle alone to 2/sex. Material was applied to shaved, abraded skin. Application sites were occluded for 6 hours/day, then rinsed and dried.

No gross lesions were observed, but microscopically thickened epidermis was noted in all animals, including the vehicle treated groups.

The sponsor concluded that 40 mg/kg/day was an appropriate high dose for the 28 day rabbit study.

6. A 28 day topical toxicity/irritancy study in the rat with mupirocin calcium cream (formulation 2172/D):
A GLP compliance statement is included in this report.
The cream formulation (2172/D) was applied to 10 Sprague-Dawley rats/sex/dose on shaved skin. Doses applied were 0 (untreated control), 0 (vehicle control), 10, 20, and 40 mg/kg/day once/day for 28 days. Additional (3) groups of 5 animals/sex were undosed/vehicle treated/40 mg/kg/day treated and maintained for a 14 day observation period.

No treatment-related effects were noted except histologically where there was a slight thickening of the epidermis, most pronounced in the vehicle control males. Thickening extended into the stratum corneum in most vehicle and cream treated animals. This finding appeared reversible as it was not seen after the recovery period.

The sponsor concluded that the vehicle caused mild skin changes in rats which were not worsened by addition of mupirocin calcium.

7. A 28 day topical toxicity/irritancy study in rabbits with mupirocin calcium cream (formulation 2172/D):
A GLP compliance statement is included in the report.
The cream formulation was applied topically to 5 New Zealand White rabbits/sex at 0 (untreated controls), 0 (vehicle controls), 10, 20, and 40 mg/kg/day for 28 days. Rabbit skin was shaved, abraded, and occluded for 6 hours with the formulation. Skin was rinsed and dried. Additional (3) groups of 2 animals/sex were untreated/treated with vehicle/treated with 40 mg/kg/d and observed for an additional 14 day recovery period. Clinical chemistries, hematology, opthalmology, body weight and feed consumption, gross necropsy were evaluated for all animals. Histopathologic examination was performed on all tissues from the high dose and controls, and skin only from all animals.

Histological thickening of the epidermis was seen in all treated animals (slight in 4/10 vehicle, 9/10 low dose, 10/10 intermediate and high dose), most prominently in vehicle treated animals (moderate thickening in 6/10 vehicle controls), some of which had minimal inflammatory cell infiltration. Lesions resolved by the end of the recovery period.

The sponsor concluded that the vehicle caused mild skin changes in rabbits which were not worsened by addition of mupirocin calcium.

Formulation BR 18319

1. Primary skin irritation study in rabbits with formulation BR 18319:
A GLP compliance statement is included in the report.
Single topical applications of 0.5 mL of cream formulation were applied to intact and abraded, shaved dorsal areas in 6 female New Zealand White rabbits. Sites were occluded for 24 hours, and reactions were assessed at 1, 24, 48 and 72 hours.

Slight erythema, with/without edema, was noted in all rabbits at the 1 hour time point. Slight erythema was still present on 3 rabbits at the 24 hour time point and 1 at the 48 hour time point.

Cream formulation BR 18319 was classified as a mild irritant to rabbit skin.

2. Primary eye irritation study in rabbits with formulation BR 18319:
A GLP compliance statement is included in the report.
Single dose application of 0.1 mL of the formulation was made to 1 eye of 3 female New Zealand White rabbits, with the untreated eye serving as the control. Eyes were not rinsed.

Irritation was graded at 1 hour, and at 1, 2, and 3 days after application.

Slight conjunctival irritation was noted in 2/3 rabbits at 1 hour, but both appeared normal at 24 hours.

Cream formulation was classified as a non-irritant to unrinsed rabbit eyes.

3. A 28 day topical irritancy study in rats with formulation BR 18319:
A GLP compliance statement is included in the report.
Topical applications of cream formulation were made daily on 5 Sprague-Dawley rats/sex at 2 g/kg/day (nominally equal to 40 mg/kg/day)/untreated/vehicle treated for 28 days.
Formulation was applied to shaved, but unabraded, unoccluded skin.

Transient erythema was observed in most treated animals, whether vehicle/mupirocin calcium. Histological examination revealed minimal epidermal thickening in all rats from the vehicle control group and 8/10 treated with mupirocin calcium.

The sponsor classified the vehicle as a slight irritant, not exacerbated by mupirocin calcium.

4. A 28 day topical irritancy study in rabbits with formulation BR 18319:
A GLP compliance statement is included in the report.
Topical applications of cream formulation were made daily on 3 New Zealand White rabbits/sex at 2 g/kg/d (nominally equal to 40 mg/kg/day)/untreated/vehicle treated for 28 days. Formulation was applied to shaved, abraded skin that was occluded for approximately 6 hours, after which the area was rinsed and dried.

Body weight gain in females of both treated groups was reduced compared to controls. Slight erythema was noted in all vehicle controls and 3/6 exposed to the complete formulation. The reaction was noted earlier and remained longer in the vehicle controls.

Histological examination revealed minimal to moderate epidermal thickening, and acute dermatitis in all treated animals. Responses were marginally more pronounced in the vehicle controls.

The sponsor classified the vehicle as a slight irritant, not exacerbated by mupirocin calcium.

Comparison Studies (21073-48, BR 18338, BR 18319)

1. A primary skin irritation study in rabbits with formulations 21073-48, BR 18338 and BR 18319:
A GLP compliance statement is included in the report.
Six shaved (3 abraded, 3 intact) areas were prepared on 6 New Zealand White rabbits. A 0.5 mL volume of each formulation was applied to one intact and one abraded area on each rabbit. Application sites were occluded for 24 hours, and reactions were assessed at 1, 24, 48, and 72 hours after dressing removal.

Significant erythema was present at all areas exposed to 21073-48 and BR 18338 at 1 hour. At

most sites after 24 hours, erythema was considered slight and was still present at 72 hours. Edema was slight to severe with BR 18338 or moderate with 21073-48 at 1 hour, and slight by 48 hours. After 72 hours, edema was still present in 8/12 areas with BR 18338 and 4/12 with 21073-48.

BR 18319 elicited erythema and edema at all sites after 1 hour, with a slight response in 10/12 at 48 hours.

The sponsor concluded that formulations 21073-48 and BR 18338 are moderate irritants, and BR 18319 is a mild irritant to rabbit skin.

2. A primary eye irritation study in rabbits with formulations 21073-48, BR 18338, and BR 18319:
A GLP compliance statement is included in the report.
Single application of 0.1 mL of each formulation was applied to one eye each of 6 female New Zealand White rabbits. In 3 animals, the eye was not rinsed. In the others, the eye was rinsed with water 4 seconds after application. Reactions were graded at 1, 24, 48, and 72 hours after application.

Irritation was confined to one eye (mild conjunctival redness) of one animal treated with 21073-48 at the 1 hour examination.

The sponsor concluded that BR 18338 and BR 18319 are non-irritants and 21073-48 is 'practically' a non-irritant, as the reaction was very mild and non-persistent.

3. A 28 day repeated application skin irritation study in the rat with 21073-48 and mupirocin ointment (mupirocin free acid in polyethylene glycol):
A GLP compliance statement is included in the report.
Five Sprague-Dawley rats/sex were clipped and had topical 21073-48/vehicle/mupirocin ointment/no treatment applied to their dorsal skin daily for 28 days. Reactions were evaluated at 24 hours after final application.

Slight erythema was noted in 5/10 vehicle treated animals and 7/10 treated with 21073-48 and 1/10 treated with the ointment. Erythema persisted for 2 days in the 3 controls and 1 cream treated animal.

Histologically, minimal epidermal thickening was noted in most animals treated with the vehicle or the cream formulation.

The sponsor concluded that the vehicle and the cream formulation are mild irritants in rats.

4. A 28 day repeated application skin irritation study in rabbits with 21073-48 and mupirocin free acid in polyethylene glycol (mupirocin ointment):

A GLP compliance statement is included in the report.
Seven male New Zealand White rabbits, shaved and abraded, were topically treated with 21073-48/vehicle alone/mupirocin ointment or were untreated. Sites were occluded for 6 hours daily, then washed and dried. Sites were evaluated 24 hours after the final application.

Vehicle application elicited the most pronounced erythema (6/7 animals), that was considered moderate in one animal. Areas exposed to 21073-48 were erythematous on 16/28 days in one rabbit, and on 8 occasions in 4 others. Mupirocin ointment produced slight erythema in 6 rabbits for up to 7 days in one animal.

Gross necropsy revealed scabbing at one vehicle treated site on one rabbit. No other lesions were noted.

Histological examination revealed minimal to mild epidermal thickening with patchy dermatitis from sites treated with vehicle or 21073-48.

The sponsor concluded that 21073 was slightly less irritating on clipped, abraded rabbit skin than was the vehicle alone, but that none of the responses were marked. Gross reactions to 21073-48 were more frequent and slightly more pronounced than those produced by mupirocin ointment.

The difference between BR 18319 and 21073-48 (intended final formulation) is that the final formulation contains % benzyl alcohol as a preservative.

ADME Studies

1. Percutaneous absorption of radioactivity in male rats with single application of ^{14}C-BR 18319:
A GLP compliance statement is included in this report.
Formulation BR 18319 was applied to shaved, intact dorsal skin of 3 male rats at 0.5 mL/kg. After 24 hours, the rats were sacrificed and radioactivity was assessed.

Excretion of radioactivity in the urine and feces was 0.18 and 0.28% of the total dose, respectively. Application site and cage contained 28% and 67% of the total dose, respectively. Percutaneous absorption was estimated at 1.6% of the applied dose.

2. Percutaneous absorption of radioactivity in rats with a single application of 14C-2172/D:
A GLP compliance statement is included in the report.
Formulation 2172/D was applied to shaved, intact dorsal skin of 3 rats/sex at 0.5 mL/kg. After 24 hours, the rats were sacrificed and radioactivity was assessed.

Excretion of radioactivity in the urine and feces was 0.1 and 0.09% of the total dose,

respectively. Application site and cage contained 52.1 and 45% of the total dose, respectively. Percutaneous absorption was estimated at 0.35% of the applied dose.

3. Percutaneous absorption of radioactivity in male rabbits with single application of ^{14}C-BR 18319:
A GLP compliance statement is included in the report.
Formulation BR 18319 was applied to shaved and abraded dorsal skin of 3 male rabbits at 0.5 mL/kg, and the application site was occluded for 6 hours. After 96 hours, the rabbits were sacrificed, and radioactivity was assessed.

Excretion of radioactivity in the urine and feces was 2.64 and 0.28%, respectively. Application site and dressings/cage contained 21.0 and 78% of the total radioactive dose, respectively. Mean percutaneous absorption was estimated at 3.4%.

4. Percutaneous absorption of radioactivity in rabbits with single application of 14C-2172/D:
A GLP compliance statement is included in the report.
Formulation 2172/D was applied to shaved and abraded dorsal skin of 3 rabbits/sex at 0.5 mL/kg, followed by occlusive dressings for 6 hours. After 96 hours, the rabbits were sacrificed and radioactivity was assessed.

Excretion of radioactivity in urine and feces was 0.69 and 0.22% of the total radioactive dose, respectively. Cage and application site contained 82.6 and 11.4% of the applied dose, respectively. Mean percutaneous absorption was estimated at 1.01%.

RECOMMENDATION:
Although the chosen market formulation appears to cause more skin irritation than the ointment, there are no significant safety concerns in the studies submitted. The application is approvable from the pharmacology/toxicology viewpoint.

Terry S. Peters, D.V.M.
VMO, HFD-520

Orig. IND
cc:
HFD-520
HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Peters
HFD-520/MO/

Concurrence Only:
HFD-520/REOsterberg 1/14/97
HFD-520/LGavrilovich
1/16/97

HFD-520/Chem/
HFD-520/CSO/D. Hanker
HFD-520/Micro/