CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-746

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 1 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 50,746
Bactroban (Mupirocin Calcium) Cream, 2%

SUBMISSION DATE: December 12, 1996

REVIEWER: Funmilayo Ajayi, Ph.D.

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

CODE: 3, s

TYPE OF SUBMISSION: Original NDA

SYNOPSIS: The above NDA was submitted for the treatment of secondarily infected traumatic skin lesions. Calcium mupirocin cream, the subject of this NDA, was investigated under IND . The sponsor conducted a percutaneous absorption study following multiple application of the cream to skin lesions as part of the data in support of this NDA. Results from this study suggested some percutaneous absorption as indicated by the detectable concentrations of monic acid in the spot urine samples collected on Days 3 and 6 of the study. Data from this study is also indicative of higher occurrence of percutaneous absorption in children (90%) compared to adults (44%). This finding is not surprising since children have greater surface area to body weight ratio compared to adults.

RECOMMENDATION: The information provided in the Human Pharmacokinetics and Bioavailability section of NDA 50,746 for Bactroban cream, 2%, is acceptable because it meets the requirements set forth in 21 CFR 320. Please pass the labeling and other relevant comments (page 3) to the sponsor.

TABLE OF CONTENTS

ORGANIZATION OF REVIEW: Following the background is a description of the drug formulation. The summary of the study is followed by the general comments and comments to the Firm.

BACKGROUND: The current NDA is for a cream formulation for the treatment of secondary skin infections such as small laceration and/or abrasions. The Bactroban[R] ointment formulation (NDA 50,591) was approved in December, 1987 and in 103 foreign countries for the treatment of skin

infections. The Bactroban[R] Nasal ointment formulation (NDA 50,703) was approved in September 1995 and in 21 foreign countries for the eradication of nasal colonization with methicillin-resistant *Staphylococcus aureus* in adults. The sponsor was urged to conduct a percutaneous absorption study following multiple application of the cream formulation to diseased skin since the percutaneous absorption of mupirocin can not be extrapolated from previous data for the nasal ointment due to the differences in the two formulations.

DRUG FORMULATION: This cream formulation contains 2% calcium mupirocin. This formulation is the same as that used in the clinical and bioavailability studies. There will be 3 sizes viz 0.5g, 15g and 30g tubes. The relative composition of the different tube sizes are comparable.

Component	% w/w
Calcium mupirocin, micronized	
Xanthan Gum	
Mineral Oil	
Cetomacrogol, 1000	
Stearyl Alcohol	
Phenoxyethanol	
Benzyl Alcohol	
Purified Water	

ANALYTICAL METHODS:

BRIEF SUMMARY OF STUDY:

Extent of percutaneous absoption through skin lesion: The absorption of mupirocin from calcium mupirocin cream, 2%, was evaluated in 10 children and 16 adults following multiple (t.i.d x 5 days) topical application to cover the entire skin lesion of interest to a uniform thickness of a dime. Urine samples were collected at approximately 2 hours after the last dose. Mupirocin was not detected in any of the urine samples. However, mupirocin is rapidly de-esterified to its microbiologically inactive metabolite, monic acid, following absorption. Elimination of mupirocin and the metabolite was previously reported to be via the kineys. The half-life of elimination of mupirocin and monic acid have been reported to be 20-40 and 30-80 minutes, respectively. Therefore, it is not surprsing that monic acid was found in the urine samples of 7 of 16 adults and 9 of 10 children who took part

in the study; indicating some percutaneous absorption of mupirocin from the cream formulation. Thus, children appeared more likely to absorb mupirocin than adults because 90% had measurable levels of monic acid in the spot urine samples compared to 44% of adults. This is consistent with the fact that children have greater surface area to body weight ratio compared to adults coupled with the knowledge that efficiency of drug absorption increases with increasing surface area of the applied dose. Although the number of subjects were limited, there was no obvious correlation between the location of lesion and monic acid excretion or age and urinary concentration of monic acid.

Gender effects: Not applicable to the current study.

Pharmacokinetic /Pharmacodynamic (PK/PD) relationship: Not applicable to the current study.

GENERAL COMMENTS (Need not be sent to Firm):

1. The systemic availability of mupirocin following topical application of the ointment and nasal ointment were demontrated to be low in previous studies.

2. Although percutaneous absorption occurred following application of the cream formulation, the measured concentrations of monic acid in the spot urine obtained approximately 2 hours after dosing are relatively low.

3. The systemic toxicology of mupirocin has been adequately investigated before approval of the ointment and nasal ointment indicating low systemic toxicity.

4. The greater absorption observed in children in terms of the number of subjects with measurable concentration of monic acid did not seem to warrant a major concern. However, the labeling for this product should reflect that a higher occurrence of percutaneous absorption in children compared to adults.

COMMENTS TO FIRM: **Please pass the following comments to the sponsor:**

An evaluation of the usefulness of *in-vitro* release rate determination for assessing post approval formulation and manufacturing changes for the 2% cream formulation is strongly encouraged.

LABELING COMMENTS:

4/1/97

Funmilayo O. Ajayi, PhD
Div. of Pharmaceutical Evaluation III

FT initialed by Frank Pelsor, PharmD.....

cc: NDA 50,746, HFD-520 (Clinical Division)
√HFD-880 (DRE3, Pelsor, Ajayi,)
HFD-340 (Viswanathan)
√CDR (Attn: B. Murphy)

Appendix I
(study summary)

STUDY TITLE: An Open-Label Study of the Percutaneous Absorption of Calcium Mupirocin Cream Applied to Skin Lesions of Children and Adults.

INVESTIGATORS AND CENTERS:

OBJECTIVES: The objective of this study was to assess whether notable percutaneous absorption of mupirocin occurs after five days of repeated application of calcium mupirocin cream (2.44%) to skin lesions.

STUDY DESIGN: This was a prospective, uncontrolled, open-label study. Subjects applied mupirocin calcium cream to skin lesions three times a day for five days and once on Day 6. Spot urine collections were taken on Day 3 and Day 6 and analyzed for the presence of mupirocin or its metabolite, monic acid. The study design did not allow for a definitive assessment of the extent of absorption of mupirocin from Bactroban^R cream.

STUDY POPULATION: Eligible subjects were male or female patients between three and twelve years of age or between eighteen and sixty-five years of age who had a skin lesion of the following type: laceration or sutured wound (size > 10 cm in length); abrasion (size > 100 cm^2); atopic dermatitis (size > 100 cm^2); eczematous dermatitis (size > 100 cm^2); or stasis dermatitis (size > 100 cm^2).
Altogether, there were nineteen adults (average age of 41 years) and ten children (average age of 8 years) enrolled in the study. Five subjects had lacerations, six had abrasions, eight had atopic dermatitis, eleven had eczema and three had stasis dermatitis.

DRUG FORMULATION: Mupirocin was supplied in 15 gram tubes as Bactroban^R Cream (2.44% mupirocin as calcium dihydrate) (Batch number B95003).

DATA ANALYSIS:

RESULTS: Concentrations of mupirocin were not quantifiable in any of the spot urine samples collected.
Monic acid was quantifiable in some of the spot urine samples, with concentrations that ranged from NQ μg/mL) to μg/mL (median value - 0.17 μg/mL) on Day 3, and from NQ μg/mL) to μg/mL (median value - 0.20 μg/mL) on Day 6. Both maximum urinary concentrations of monic acid on Day 3 μg/mL) and Day 6 μg/mL) were observed in subject
Monic acid was quantifiable in the spot urine samples from six of sixteen adults (37.5%) on Day 3, five of fifteen adults (33%) on Day 6, seven of ten children (70%) on Day 3 and eight of ten

children (80%) on Day 6. Overall, seven of sixteen adults (43.8%) and nine of ten children (90%) had quantifiable monic acid.
The total wound areas and amounts of Bactroban^R cream applied differed widely between the subjects, and there did not appear to be any obvious relationship between these and the urinary concentrations of monic acid present.

CONCLUSIONS: Measurable concentrations of mupirocin were not present in any of the urine samples collected. This finding is not surprising since the elimination half-life of mupirocin is very short. However, absorption of mupirocin from topically applied Bactroban^R cream can be said to occur in some subjects since measurable concentrations of monic acid were present in some of the spot urine samples. Measurable monic acid concentrations occurred more in children compared to adults. However, the degree of percutaneous absorption following multiple dosing, appear to be very minimal in the studied adult and children population indicating little or no safety implication.

COMMENTS: Although both maximum urinary concentrations of monic acid on Day 3 μg/mL) and Day 6 μg/mL) were observed in subject (47-year old), the wound area (116 cm^2) and the dose (464 mg) applied are within the observed range for the other subjects in the study. In fact, the next high monic acid concentration μg/mL) was observed in subject (3-year old) who had the largest wound area (1350 cm^2) and received the highest dose (1202 mg).
Although there were protocol violations with respect to dosing information and urinary collection for subject (48-year old) the Day 3 urinary monic acid concentration was accepted because the value is within the observed range and did not have a major influence on the outcome of the study.
Although monic acid was present in the urine of 90% children compared to 44% adults, the observed concentrations in the children μg/mL) are within the range μg/mL) observed in the adult population.

Total Mupirocin Dose Administered and Urine Concentrations of Monic Acid on Days 3 and 6 of Repeated Topical Administration

Subject No.	Age (years)	Total Wound Area (cm^2)	Total Bactroban® Cream applied (g)	Total Mupirocin Dose (mg)	Day 3 Time Between Last Applied Dose and Urine Collection	Day 3 Urinary Monic Acid Conc (ug/mL)	Day 6 Time Between Last Applied Dose and Urine Collection	Day 6 Urinary Monic Acid Conc (ug/mL)
Adults								
	56	132	15.4	308	2 hr	NQ	1 hr 55 min	NQ
	47	116	23.2	464	2 hr	10.034	1 hr 55 min	0.731
	60	228	16.4	328	2 hr	NQ	2 hr	NQ
	38	156	12.2	244	2 hr	NQ	2 hr	NQ
	29	19	12.7	254	1 hr 55 min	NQ	2 hr	NQ
	45	216	14.2	284	2 hr	NQ	2 hr	NQ
	40	374	16.1	322	2 hr 2 min	NQ	1 hr 58 min	NQ
	47	107	13.5	270	2 hr	NQ	2 hr	NQ
	48	11	15.0	300	1 hr 50 min	NQ	2 hr	NQ
	34	58	14.8	296	1 hr 59 min	0.206	2 hr	0.310
	46	118	12.6	252	2 hr	0.080	2 hr	NQ
	34	99	11.8	236	2 hr	NQ	2 hr	NQ
	31	102	24.0	480	1 hr 45 min	NQ	1 hr 45 min	0.101
	32	144	14.7	294	2 hr	0.064	2 hr	0.128
	48	525	NA	NA	NA	0.351	NS	NS
	30	500	18.1	362	5 hr 25 min	0.167	1 hr 30 min	0.253
Children								
	6	106	27.3	546	2 hr	0.146	2 hr	NQ
	12	194	19.6	392	2 hr	0.400	1 hr 50 min	0.696
	12	122	11.9	238	2 hr	0.102	2 hr	0.176
	9	159	10.7	214	1 hr 59 min	0.116	2 hr	0.203
	11	100	12.7	254	1 hr 45 min	0.161	2 hr	0.187
	10	58	9.4	188	2 hr	NQ	2 hr	NQ
	3	1350	60.1	1202	2 hr 10 min	1.295	10 min	0.418
	6	100	24.1	482	2 hr 19 min	0.261	2 hr	0.098
	3	140	16.8	336	2 hr 36 min	NQ	2 hr 25 min	0.066
	12	180	33.8	676	2 hr 35 min	NQ	2 hr 17 min	0.523

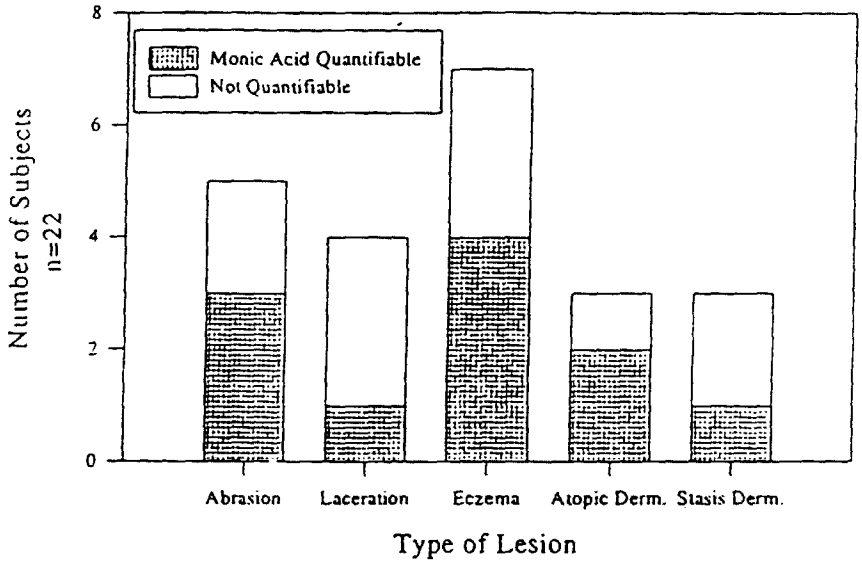
No quantifiable concentrations of mupirocin (LLQ < 0.05 ug/mL) were found in any of the spot urine samples.

NA = Not available, NS = No sample

NQ = Not quantifiable, lower than the limit of quantification (i.e. < 0.05 ug/mL)

Figure 1
Subjects With and Without Quantifiable Urinary Monic Acid Compared to Lesion Type

Adults



Children

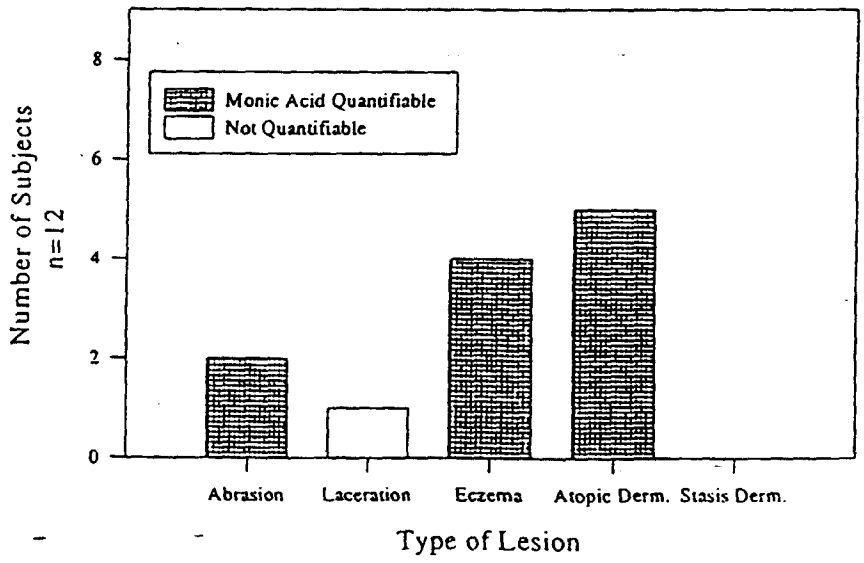
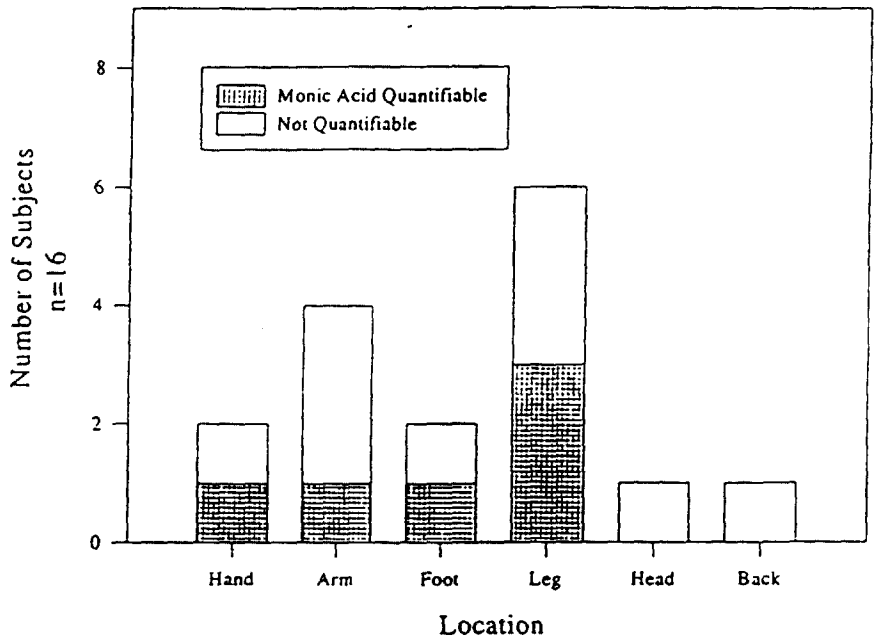


Figure 2
Subjects With and Without Quantifiable Urinary Monic Acid Compared to Lesion Location

Adults



Children

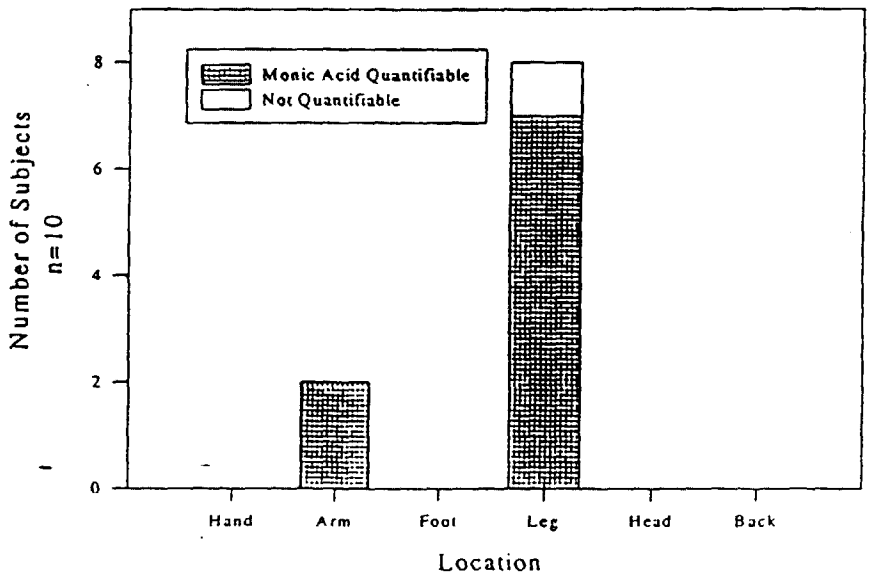
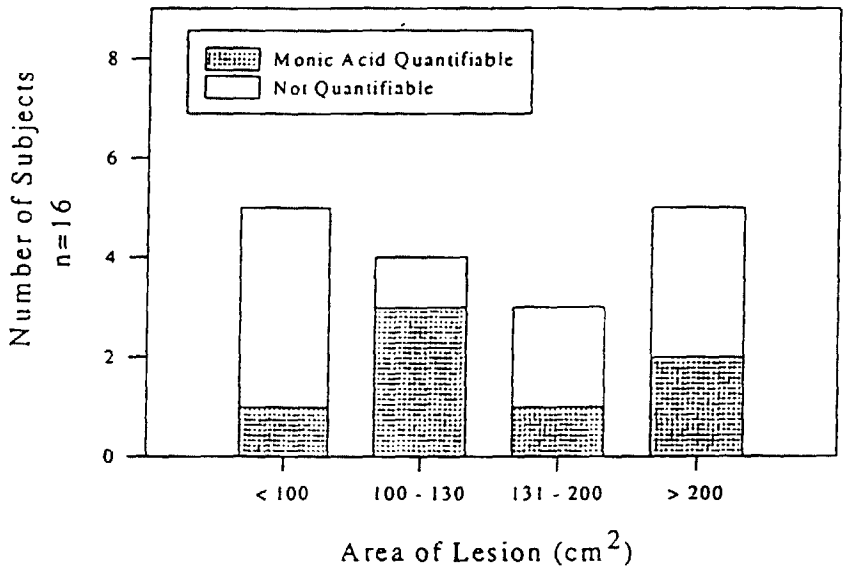


Figure 3
Subjects With and Without Quantifiable Urinary Monic Acid Compared to Total Lesion Area

Adults



Children

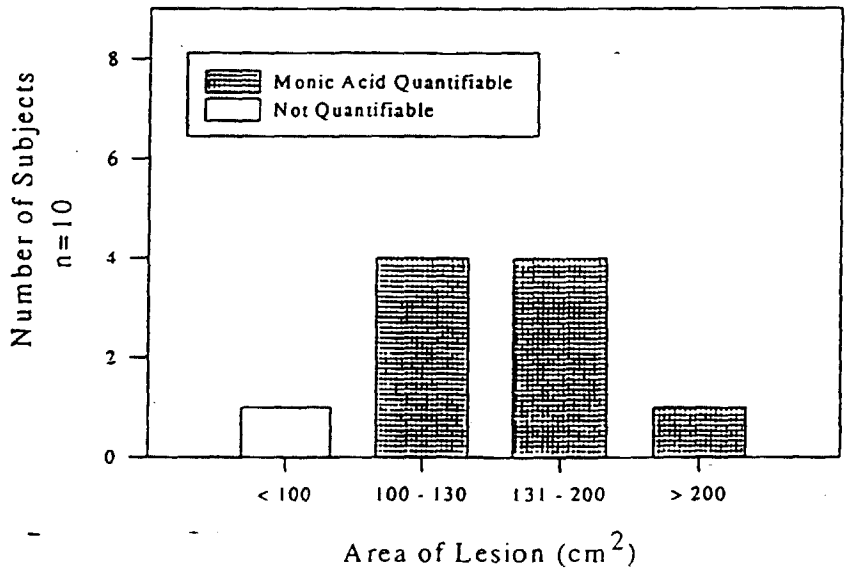
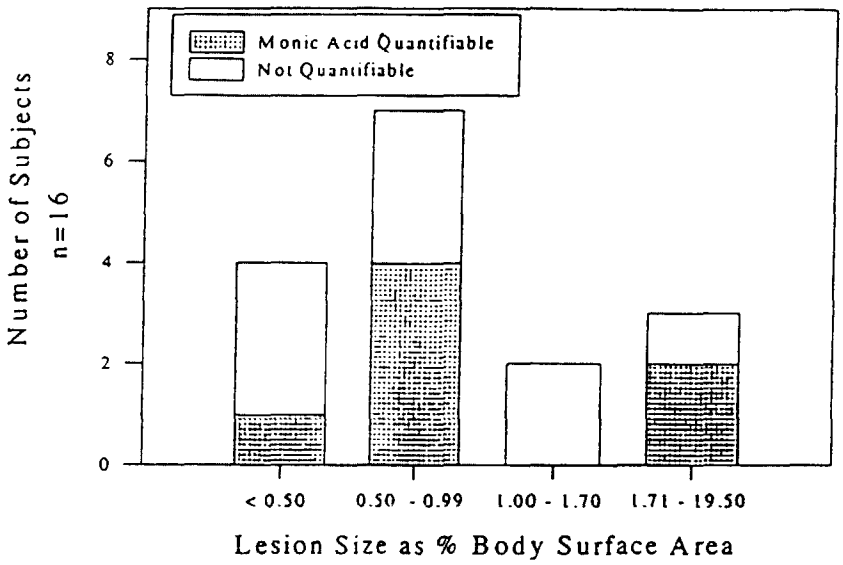


Figure 4

Subjects With and Without Quantifiable Urinary Monic Acid Compared to Lesion Size as a Percentage of Body Surface Area

Adults



Children