CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-746

MICROBIOLOGY REVIEW(S)

NDA 50-746
Bactroban
SKB

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1

NDA # 50-746 DATE COMPLETED: 10 March, 1997

APPLICANT(NDA):

SMITHKLINE BEECHAM PHARMACEUTICALS
One Franklin Plaza
Box 7929
Philadelphia, PA 19101

CHEM/THER. TYPE: Topical

SUBMISSION REVIEWED: CANDA 50-746
PROVIDING FOR: Clinical and Microbiological Studies in support of labeling claims for secondary infections of the skin

PRODUCT NAMES(S):

Proprietary: Bactroban®

Non-Proprietary/USAN: Mupirocin calcium

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.
Chemical Name: Calcium 9-[(E)-(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxypyran-2-yl]-3-methylbut-2-enoyloxy]nonanoate, dihydrate

Molecular Formula: $(C_{52}H_{86}O_{18})_2Ca \bullet 2H_2O$

Molecular Weight: 1075.3

DOSAGE FORMS(S) Cream

STRENGTHS: 2%

ROUTE(S) OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Antiinfective

DISPENSED: X Rx ___ OTC

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INITIAL SUBMISSION:
Received by CDER: 12/13/96
Received by Reviewer: 1/9/97
Review Completed: 10 March, 1997

AMENDMENT(S)
Received by CDER: N/A
Received by Reviewer:
Review Completed:

REMARK(S):

From the microbiological perspective, this application involves no new basic microbiological information. This application provides microbiological labeling which is conceptually identical to a currently approved mupirocin product. While the approved product is labeled primarily for treatment of impetigo due to staphylococci and Lancefield's Group A streptococci, this application proposes treatment of infections with the same organisms secondary to trauma. This New Drug Application was examined for any factors which would have an impact on this new treatment modality using a new dosage form. No such factors were found. However, there are concerns which may have a significant impact on the use of mupirocin in the future.

Future concerns relate to potential increases of resistance among populations of staphylococci and streptococci. Currently, two levels of resistance have been noted in existing labeling. One level of resistance occurs around an MIC range of micrograms per millliliter while the other level of resistance occurs around micrograms per milliliter. These resistance levels are expressed as ranges because susceptibility testing for mupirocin has not been standardized. The lower resistance level has been generally discounted as being a significant level of resistance due to the overwhelming concentrations of mupirocin theoretically available at the site of infection. However, the higher mupirocin resistance level is associated with other factors in the relationship between host and pathogen. Particularly, mupirocin is highly protein bound to a sufficient magnitude that the intrinsic high activity of mupirocin at a topical infection site may not be so overwhelming. Unfortunately, there is no current systematic source of data from studies designed to examine the regional distribution of this high level of mupirocin resistance. In the absence of these data, there is no basis for regulatory restrictions for usage of mupirocin. The Microbiology subsection of the labeling reflects this uncertainty in the approved product for impetigo as well as the proposed product for infections secondary to trauma.

The pertinent microbiological data in support of this application included many studies previously submitted to earlier approved applications. Obviously, these data continue to support the labeling

statements approved earlier by the FDA. Since no conceptual labeling changes were proposed for this application by the applicant, these studies also support the proposed labeling for this application. These data were summarized by the applicant in the submission and presented in both written and electronic format. Selected portions of the electronic format were edited and incorporated into the technical Microbiological Review Notes shown below.

Subsequent to analysis of the data in support of this application, the proposed labeling was drafted to accommodate the applicable general format and content prescribed by the NDA Holders' Letter (HL) of 1993. The FDA proposed draft of the Microbiology subsection of the package insert is shown below in the Conclusions section of this review.

CONCLUSIONS and/or RECOMMENDATIONS:

From the microbiological perspective, this application is approvable pending submission of the following text:

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Microbiological Review Notes:

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INTRODUCTION

Mupirocin is produced by submerged fermentation of *Pseudomonas flourescens* NCIB 10856. Mupirocin was previously known as pseudomonic acid A and is referred to as such in earlier study reports and literature. Mupirocin is the first antibacterial agent in a new class of antibacterial agents. Initially, mupirocin appeared to have a wide antibacterial spectrum against Gram-positive and Gram-negative bacteria, particularly against Gram-positive cocci and certain Gram-negative bacteria such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. It was less effective against other Gram-negative bacteria.

Mupirocin is rapidly metabolized *in vivo* to an antibacterially inactive compound, monic acid. This metabolization leads to serum antibiotic concentrations of insufficient duration following oral administration to human volunteer subjects for further progression as a systemic antibiotic. Mupirocin has therefore been developed for topical antibacterial therapy. Mupirocin ointment, formulated as 2% w/w mupirocin in a polyethylene glycol base ('Bactroban', approved in 1987) has been used successfully in the treatment of common bacterial skin infections, such as impetigo, folliculitis and furunculosis, caused by Staphylococcus aureus (including methicillin-resistant strains), other staphylococci and pyogenic streptococci. Mupirocin calcium, formulated as 2% w/w mupirocin in a soft white paraffin base, is approved in the United States for the eradication of nasal colonization with methicillin-resistant S. aureus (MRSA).

PRECLINICAL EFFICACY

In vitro

Mechanism(s) of Action.

Broadly speaking, mupirocin primarily inhibits both protein and RNA synthesis in *S. aureus*. These inhibitions were later found to be dependent on the specific target of mupirocin, isoleucyl-tRNA synthetase (Ile-tRNA synthetase). Mupirocin was shown to be a potent inhibitor of electrophoretically pure Ile-tRNA synthetase, and had little or no inhibitory effects on other tRNA synthetases.

Ile-tRNA synthetase catalyses the formation of isoleucyl-tRNA in two discrete stages through the formation of an enzyme-isoleucyladenylate complex. Mupirocin is a competitive inhibitor with isoleucine for the formation of the enzyme-Ile-AMP complex and has no effect on the transfer of isoleucine from the enzyme-Ile-AMP complex to tRNA. Mupirocin has a greatly reduced affinity for mammalian Ile-tRNA synthetase.

Antimicrobial Spectrum of Activity.

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The antibacterial spectrum of activity of mupirocin calcium dihydrate salt was compared with mupirocin lithium and mupirocin sodium against typical aerobic Gram-positive cocci; it was also compared with mupirocin lithium reference material against Gram-negative bacteria. The results are illustrated in Tables 1 and 2, respectively. The data show that the salts of mupirocin exhibit similar in vitro antibacterial activity.

Table 1 Antibacterial activity of mupirocin (calcium salt) BRL 4910F, compared with mupirocin (sodium salt) BRL 4910 and mupirocin (lithium salt) BRL 4910B against Gram-positive cocci (Report: PB-0021/BRL 4910/1)

	MIC (mcg/ml) range		
Organism (N)	BRL 4910F	BRL 4910	BRL 4910B
S. aureus (13)			
S. epidermidis (4)			
S. saprophyticus (4)			
S. pyogenes (3)			
S. pneumoniae (3)			

Table 2 Antibacterial activity of mupirocin (calcium salt) BRL 4910F, compared with mupirocin (lithium salt) BRL 4910B against a range of Gram-negative bacteria (Report: PB-0012/BRL 4910/1)

Organism (N)	MIC (mcg/ml) range	
	BRL 4910F	BRL 4910B
E. coli (5)		
K. pneumoniae (3)		
P. mirabilis (4)		
M. morganii (3)		
P. rettgeri (2)		
S. marcescens (3)		
Enterobacter species (3)		
P. aeruginosa (5)		

Further *in vitro* susceptibility studies (Table 3) revealed that the growth of staphylococci and streptococci was inhibited by concentrations of mupirocin calcium MIC <1.0 mcg/ml) while isolates of *Enterococcus faecalis* were less susceptible with MIC's >32-64 mcg/ml as were the test strains of corynebacteria with MIC's >128 mcg/ml. The anaerobic Gram-positive bacteria, *Peptostreptococcus anaerobius* and *Peptococcus asaccharolyticus* were not inhibited by 128 mcg/ml, and the MIC for *Clostridium* species and *Propionibacterium acnes* was >1024 mcg/ml.

Table 3 Antibacterial spectrum of mupirocin (calcium salt), BRL 4910F compared with mupirocin (lithium salt) BRL 4910B against a range of Gram-positive bacteria (Report: PB-0013/BRL 4910/1)

Organism	MIC (mcg/ml)	
	BRL4910F	BRL4910B
Staphylococcus aureus ATCC 25923	0.5	0.5

Staphylococcus aureus NCTC 11561	0.25	0.25
Staphylococcus epidermidis 54815	0.25	0.25
Staphylococcus saprophyticus Novo 20	0.25	0.25
Staphylococcus haemolyticus NCTC 11042	0.5	0.25
Staphylococcus hominis BW	0.5	0.5
Staphylococcus capitis NCTC 11045	0.06	0.06
Staphylococcus cohnii NCTC 11041	0.12	0.12
Micrococcus luteus ATCC 4698	>1024	>1024
Micrococcus varians ATCC 15306	>1024	>1024
Micrococcus nishinomyaenosis ATCC 29093	>1024	>1024
Streptococcus pyogenes 421	0.12	0.12
Streptococcus agalactiae 9579	0.12	0.12
Streptococcus species, Group C 2465	0.25	0.25
Streptococcus species, Group G 2373	0.25	0.25
Streptococcus durans 98-D	32	32
Streptococcus bovis 1383	128	128
Streptococcus pneumoniae 1660	0.5	0.25
Streptococcus mitis 1324	0.25	0.25
Enterococcus faecalis ATCC 29212	64	64
Enterococcus faecium 2583	32	32
Erysipelothrix rhusiopathiae Standing	16	16
Listeria monocytogenes NCTC 5348	16	16
Corynebacterium xerosis 9755	>128	>128
Corynebacterium minutisimum B120	>128	>128
Corynebacterium Group JK	>128	>128
Bacillus subtilis ATCC 6633	0.25	0.25
Peptostreptococcus anaerobius 290.5	>128	>128
Peptostreptococcus asaccharolyticus 546	>128	>128
Clostridium difficile 25665	>1024	>1024
Clostridium sporogenes 532	>1024	>1024
Clostridium tertium 2917	>1024	>1024
Propionibacterium acnes KN 160	>1024	>1024
Propionibacterium granulosum KN 165	>1024	>1024
Propionibacterium avidum VPI 0575	>1024	>1024

Table 4 shows the activity of mupirocin salts against selected Gram-negative bacteria. In general, the majority of Gram-negative bacilli required high concentrations of mupirocin for inhibition of growth.

Table 4. Antibacterial spectrum of mupirocin (calcium salt) BRL 4910F compared with mupirocin (lithium salt) BRL 4910B against Gram-negative bacteria (Report: PB-0013/BRL 4910/1)

Organism	MIC (mcg/ml)	
	BRL 4910F	BRL 4910B
Haemophilus influenzae Q1	0.06	0.06

Neisseria gonorrhoeae WHO V	0.06	0.06
Pasteurella multocida 1633	0.12	0.12
Escherichia coli NCTC 10418	128	128
Klebsiella pneumoniae A	128	128
Klebsiella oxytoca 1082E	256	256
Proteus mirabilis 889	128	128
Proteus vulgaris X	128	128
Providencia stuartii Harding	32	32
Enterobacter cloacae NCTC 10005	32	32
Enterobacter aerogenes T660	128	128
Citrobacter freundii W18	128	128
Providencia rettgeri B	>1024	>1024
Morganella morganii F	>1024	>1024
Serratia marcescens US9	>1024	>1024
Acinetobacter anitratus WIG 1	>1024	>1024
Pseudomonas aeruginosa R3	>1024	>1024
Bacteroides fragilis BC4	>1024	>1024

In a study by Thornsberry (Report: BRL-004910/RSD-100DF6/1) the in vitro activity of mupirocin was compared with cephalothin against *H. influenzae, M. catarrhalis, S. pyogenes, S. epidermidis, S. saprophyticus* and *S. pneumoniae*. The results of the study are presented in Table 5. Mupirocin demonstrated activity against most isolates tested. No cross-resistance was seen with beta-lactamase positive, or ampicillin resistant *H. influenzae*, methicillin-resistant *S. epidermidis* or penicillin-resistant *S. pneumoniae*. In contrast, cephalothin demonstrated high MICs against the isolates of ampicillin-resistant *H. influenzae*, and penicillin-resistant *S. pneumoniae*.

Table 5 The activity of mupirocin and cephalothin against selected species.

		Mupirocin		Cephalothin	
Species	N	Range	MIC90	Range	MIC90
H. influenzae	107		0.25		64
abeta-lac+	32		0.12		64
bbeta-lac- ampS	63		0.25		8
cbeta-lac- ampI	2		0.25		128
dbeta-lac- ampR	10		0.12		128
M. catarrhalis	97		1		8
S. pyogenes	100		0.12		0.12
S. epidermidis	103		0.25		0.5
eMSSE	86		0.25		0.25
fMRSE	17		8		0.5
S. saprophyticus	100		0.25		1
S. pneumoniae	109		0.5		8
gpenS	63		0.25		0.25
hpenI	29		1		8
ipenR	17		1		32
TOTAL	616		1		8

The comparative activities of the mupirocin lithium and mupirocin calcium dihydrate salts against methicillin-susceptible and methicillin-resistant strains of *Staphylococcus aureus*, are shown in Table 6. The

results demonstrate that the activities of the individual salts were virtually identical. Likewise, the activities of the two mupirocin salts against isolates of coagulase-negative staphylococci were also the same, or within one two-fold dilution (Reports:MY-1005/BRL-00491/1).

Table 6 Antibacterial activity of mupirocin calcium (BRL 4910F) compared with mupirocin lithium (BRL 4910B) against 35 isolates of methicillin-susceptible *S. aureus* (Report: PB-0013/BRL4910/1)

	MIC (mcg/ml) and number of strains inhibited							
	0.06	0.12	0.25	0.5	1	2	4	8
BRL 4910F	2	8	17	8				
BRL 4910B	2	9	15	9				
Methicillin				2	8	22	3	

Table 7 Antibacterial activity of mupirocin calcium (BRL 4910F) compared with mupirocin lithium (BRL 4910B) against 24 isolates of methicillin-resistant *S. aureus* (Report: PB-0013/BRL4910/1)

	0.06	0.12	0.25	0.5	1	2	4	³8
BRL4910F		11	13	8				
BRL 4910B		8	16	9				
Methicillin								24

Shortly before the nasal formulation of mupirocin was introduced, a study was conducted in 1993, comparing the susceptibilities of nasal with non-nasal *S. aureus* isolates to mupirocin, fusidic acid, neomycin, bacitracin, erythromycin and chlorhexidine (Report: MY-1005/BRL-004910/1). A total of 1000 randomly selected *S. aureus* isolates were obtained (414 nasal and 586 non-nasal isolates). The MIC90s for the 1000 isolates were: 0.5 mcg/ml for mupirocin and fusidic acid; 1.0 mcg/ml for chlorhexidine; 16 mcg/ml for bacitracin; 32 mcg/ml for neomycin; and >128 mcg/ml for erythromycin. The MIC90s, MIC ranges, and numbers of isolates with MICs of > 4 mcg/ml for the 1000 isolates, the MRSA and the MSSA isolates are shown in Tables 8, 9 and 10, respectively.

Table 8 Comparison of MICs for 1000 *S. aureus* isolates

	MIC90 (mcg/ml)	MIC Range (mcg/ml)	# with MICs >4 mcg/ml
Mupirocin	0.5		9
Neomycin	32		227
Bacitracin	16		827
Erthromycin	>128		339
Fusidic acid	0.5		4
Chlorhexidine	1.0		0

Table 9 Comparison of MICs for 222 MRSA isolates

MIC90 (mcg/ml)	MIC Range (mcg/ml)	# with MICs >4mcg/ml

Mupirocin	0.5	9
Neomycin	128	190
Bacitracin	16	197
Erythromycin	>128	204
Fusidic acid	0.5	2
Chlorhexidine	1.0	0

Table 10 Comparison of MICs for 778 MSSA isolates

	MIC90 (mcg/ml)	MIC Range (mcg/ml)	# with MICs >4mcg/ml
Mupirocin	0.25		0
Neomycin	0.5		37
Bacitracin	16		630
Erythromycin	>128		135
Fusidic acid	0.5		2
Chlorhexidine	1.0		0

Mechanism(s) of Resistance Studies (Panel).

Enzyme Hydrolysis Rates
In studies involving strains of *S. aureus* and *S. epidermidis* exhibiting varying levels of mupirocin resistance, Cookson (Cookson B. Failure of mupirocin-resistant staphylococci to inactivate mupirocin. European Journal of Microbiology and Infectious Disease. 8:1038-1040 (1989)) was unable to show any apparent destruction or inactivation of mupirocin after exposure to intact cells or to disrupted cell extracts, as determined by a variety of assay techniques, including HPLC and comparative disk diffusion. Likewise, using a larger number of strains of *S. aureus* exhibiting a wider range of resistances to mupirocin, Farmer et al. (Report: APS-10/BRL4910/1; Volume 1.013/page 000132) were unable to demonstrate by assays, any enzymatic degradation or modification of mupirocin after exposure to cell-free supernatants. These authors found that there was a significant correlation between the concentration of mupirocin required to inhibit the isoleucyl-tRNA synthetase and the level of resistance expressed by the organism. They concluded that the production of a modified isoleucyl-tRNA synthetase was responsible for mupirocin-resistance among the strains of *S. aureus* studied.

Epidemological Studies (Published Literature).

High level resistance to mupirocin has indeed been observed. However, this high level resistance has certainly not been broadly reported among populations of staphylococci. Only one report emerged from a Medline search for "mupirocin resistance" in which quantitative statements were made about the incidence of resistance. The report's citation and abstract are shown below.

Record 19 of 34 - MEDLINE EXPRESS (R) 1991-1995
TI: Mupirocin resistance in methicillin-resistant *Staphylococcus aureus* from a veterans hospital.
AU: Naguib-MH; Naguib-MT; Flournoy-DJ
SO: Chemotherapy. 1993 Nov-Dec; 39(6): 400-4
ISSN: 0009-3157

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LA: ENGLISH

AB: 679 clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA) which occurred from 1986 and 1992 were retrospectively tested to determine the frequency of mupirocin resistance. With disk agar diffusion screening, 26 of 679 MRSA had zones of inhibition of < 18 mm using a 5 micrograms mupirocin disk. Minimal inhibitory concentrations (MICs) by agar dilution on the 26 suspect MRSA revealed that 9 were resistant. Of these 9, 1 had a MIC of 6.25, 4 of 12.5, 1 of 25, 1 of 500 and 2 of > 1,000 micrograms/ml. Although the overall incidence of mupirocin resistance was low in our hospital, 5 of the 9 resistant isolates occurred in 1992 and may signal a much more serious threat in the future.

AN: 94038222

It should be noted that only three of the resistant isolates could be considered to have high level resistance. Although high level resistance has been demonstrated in staphylococci, there is a paucity of peer-reviewed publications reflecting a significant frequency of high level resistance. Of course, this observation should be taken in the context that high level resistance may be emerging, but its frequency among clinical isolates is not yet a major threat to the utility of mupirocin. Indeed, high level resistance is plasmid-borne. Clearly, protracted and wide-spread selective pressure through overuse may certainly and quickly reverse the future assessment of the utility of mupirocin.

CLINICAL EFFICACY

Clinical Microbiology

Isolates/relevance to approved indications.

All gram positive pre-therapy pathogens were eradicated, suggesting that clinically significant resistance to mupirocin did not occur. It should be noted that none of the pathogens present at end of therapy (EOT) or followup (FU) in mupirocin treated patients was a gram positive organism. While mupirocin is active against many of the common gram positive skin pathogens, it has limited activity against gram negative pathogens. It is not surprising that all intent to treat (ITT) bacteriological failures in the mupirocin group were attributed to gram negative pathogens.

Bacteriological Efficacy

Correlation of Test Results with Outcome

Statistics.

As noted above, all gram positive pre-therapy pathogens were eradicated, suggesting that clinically significant resistance to mupirocin did not occur. It should be noted that none of the pathogens present at EOT or FU in mupirocin treated patients was a gram positive organism. While mupirocin is active against many of the common gram positive skin pathogens, it has limited activity against gram negative pathogens. It

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is not surprising that all ITT bacteriological failures in the mupirocin group were attributed to gram negative pathogens.

Package Insert.

Isolates Approved
See proposed labeling in Conclusions section.

7/2/97

James R. King
Microbiologist, HFD-520

SMicro/ASheldon

DepDir/LGavrilovich

cc: Orig. NDA # 50-746
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon BD#1 and Final Init. 7/1/97 ASO 7/5/97
HFD-502
HFD-520 7/10/97
HFD-520/Micro/King
HFD-520/MO/Bostwick
HFD-520/Pharm/Peters
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker

Printed for signatures on 02 JUL 97