

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-788

MICROBIOLOGY REVIEW(S)

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

NDA # 50-788

DATE COMPLETED: October 31, 2002

APPLICANT:

Clay-Park Labs, Inc.
1700 Bathgate Ave.
Bronx, NY 10457

CHEM/THER. TYPE: Topical Antibiotic

SUBMISSION REVIEWED:

PROVIDING FOR: Clinical and Microbiological Studies in support of labeling claims for topical treatment of impetigo caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.

PRODUCT NAME:

Proprietary: Mupirocin Ointment , 2%

Non-Proprietary/USAN:

CHEMICAL NAME, MOLECULAR FORMULA, MOL. WT.

Chemical Name: (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

Molecular Formula: C₅₂H₈₆O₁₈

Molecular Weight: 500.63

DOSAGE FORM: Cream containing castor oil

STRENGTH: 2%

ROUTE OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Antiinfective

DISPENSED: Rx

INITIAL SUBMISSION:

Received by CDER: 3/7/02

Received by Reviewer: 10/4/02

Review Completed: October 31, 2002

REMARKS:

From the microbiological perspective, the application provided no new basic microbiological information. What is presented by the applicant is mainly based on literature references used to approve previous Mupirocin products. This application provides microbiological labeling which is similar to that of currently approved mupirocin products. Concerning *invitro* susceptibility studies, references are mainly from the British literature and limited to the early to mid 1980s. Recent references discuss the appearance in patients of increasing numbers of mupirocin resistant isolates of staph and subsequent treatment failures. While the approved products are labeled for treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*,

, this New Drug Application is for impetigo only.

Concerns in this review relate to increases of resistance among populations of staphylococci observed since filing of the last approved mupirocin product. Two levels of mupirocin resistance have been observed in *S. aureus* isolates, a low level of resistance is defined as an MIC level beginning at 4 but < 100 micrograms per milliliter while the high level of resistance is defined as > 500 micrograms per milliliter (Infect. Contro Hosp Epidemiology 1995; 16:354-358). These resistance levels are usually expressed as ranges because susceptibility testing for mupirocin has not been standardized. There is a broad range in MIC levels and other investigators have presented ranges differing by one or more two-fold dilutions. Although the lower resistance level has been generally discounted as being of clinical significance due to the overwhelming concentrations of mupirocin theoretically available at the site of infection there have been a few clinical failures at this low MIC level. The higher mupirocin resistance level is more commonly associated with decreased clinical efficacy and has been implicated in several hospital epidemics.

Mupirocin is highly protein bound, 97% in blood, which is of sufficient magnitude to question whether the intrinsic high activity of mupirocin at a topical infection site may not be so overwhelming as to always overcome even lower level mupirocin resistant Staphylococci. A further complication is the common finding of the linking of mupirocin resistance with isolates. The recommended microbiology subsection of the labeling will reflect these new resistance findings by recommending changes in the applicant's proposed package insert.

The applicant previously agreed to remove, " from the first sentence of the microbiology section of the package insert as mupirocin resistance is often linked to methicillin (as shown in the discussion of the Sentry resistance Survey, discussed in the technical section of the review, Mupirocin and Methicillin resistance occur together 17 % of the time in *S. aureus* and 38% of the time in CONS) resistance as demonstrated by the oxacillin disk reaction. In addition to the

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applicant's proposed changes, this reviewer is proposing the following changes to the package insert:

1. For list one, the language will be changed to reflect the finding of significant numbers of mupirocin resistant isolates to read, "Mupirocin has been shown to be active against susceptible strains of *S. aureus* and *S. pyogenes* both *invitro* and in clinical studies."
2. Resistance testing is usually recommended for *S. aureus*. Mupirocin products should not be used in situations where *Staphylococcus aureus* has been shown to give a positive oxacillin disk reaction.
3. New genetic and biochemical findings have more clearly defined the mechanism of action and the mechanism of resistance to Mupirocin. These findings will be reflected in changes to the appropriate parts of the microbiology section of the package insert.
4. The second and third sentences of the package insert will be eliminated since the antibiotic

New *invitro* data concerning the spectrum of activity of mupirocin has not appeared in the scientific-medical literature in the past few years and new studies were not submitted by the applicant. Because of this lack of new documented studies, data defining the spectrum of activity of mupirocin in the technical section of the microbiology review will be taken from previous studies. However recent data and analysis concerning the mechanism of action, mechanism of resistance and decreased activity due to mupirocin resistant Staphylococci will be presented in the appropriate sections of the review.

CONCLUSIONS and RECOMMENDATIONS:

From the microbiological perspective, this application is approvable pending submission of the following text for the microbiology section of the package insert:

Microbiology:

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. Its spectrum of activity includes gram-positive bacteria. It is also active, *invitro* only, against certain gram-negative bacteria.. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobial agents.

When mupirocin resistant isolates occur, they result from the production of a modified isoleucyl-tRNA synthetase or, the acquisition, by genetic transfer, of a plasmid mediating a new isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >500 mcg/mL) has been reported in increasing numbers of isolates of *S. aureus* and with higher frequency in coagulase-negative staphylococci. Methicillin resistance and mupirocin resistance commonly occur together in *S. aureus* and *Coagulase Negative Staphylococci*.

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Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally eight-fold to thirty-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the activity of mupirocin has not been determined.

Mupirocin has been shown to be active against susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*, both *in vitro* and in clinical studies. (See INDICATIONS AND USAGE Section).

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INTRODUCTION:

Mupirocin is produced by submerged fermentation of *Pseudomonas fluorescens* NCIB 10856. Mupirocin was previously known as pseudomonic acid A and is referred to as such in earlier study reports and literature. Mupirocin represents a new class of antibacterial agents. Initially, mupirocin appeared to have a wide antibacterial spectrum with good activity against Gram-positive and Gram-negative bacteria, particularly against Gram-positive cocci including Streptococci and Staphylococci and Gram-negative bacteria such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Mupirocin was later shown to be less active against other Gram-negative bacteria including the enterobacteriaceae, other gram-positive bacteria, anaerobes and fungi.

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 volunteers to warrant development as a systemic antibiotic. Mupirocin has therefore been developed as a topical antibacterial therapeutic. 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* 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

Mechanism(s) of Action

Mupirocin was shown to inhibit protein, RNA and cell-wall 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 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:

In vitro susceptibility studies (Table 1) 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. Mupirocin is inactive invitro against *P. aeruginosa*, anaerobes, fungi, and the Enterobacteriaceae. An important feature of Mupirocin's invitro activity is it's relative lack of activity versus members of the normal skin flora, *Micrococcus*, *Corynebacterium* and *Propionobacterium* spp. These skin commensals protect the skin against pathogens.

Table 1 Taken from: Antibacterial spectrum of mupirocin (Mandel, Douglas, Bennett's Principles and Practice of Infectious Diseases, Fifth Edition, 2002, Churchill Livingstone, New York, Edinburgh, London, Philadelphia, p. 432 and Antimicrobial Agents and Chemotherapy, volume 27, 1985, p. 495-498 Sutherland, et. al.)

Organism	MIC (mcg/ml)
Staphylococcus aureus ATCC 25923	0.12
Staphylococcus epidermidis 54815	0.5
Staphylococcus saprophyticus Novo 20	0.25
Micrococcus luteus ATCC 9341	>1024
Streptococcus pyogenes 421	0.12
Streptococcus agalactiae 9579	0.5
Streptococcus pneumoniae I	0.5
Streptococcus sanguis	1.0
Enterococcus faecalis I	64
Enterococcus faecium 2583	32
Erysipelothrix rhusiopathiae	8
Listeria monocytogenes NCTC 5348	8
Corynebacterium xerosis 9755	>128
Corynebacterium Group JK	>128
Bacillus subtilis ATCC 6633	0.25
Bacillus anthracis NCTC 8234	64
Peptostreptococcus prevoti 372.5	>128
Clostridium difficile 12328	32
Clostridium sporogenes 532	>1024
Propionibacterium acnes 10162	>128

Table 2 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.

Table2 . Antibacterial spectrum of mupirocin against Gram-negative bacteria

Organism	MIC (mcg/ml)
Haemophilus influenzae Q1	0.06
Neisseria gonorrhoeae WHO V	0.06
Neisseria meningitidis 1990	0.05
Moraxella catarrhalis 1520	0.2
Pasteurella multocida 1633	0.12
Escherichia coli NCTC 10418	128
Klebsiella pneumoniae A	128
Klebsiella oxytoca 1082E	256
Proteus mirabilis 889	128
Proteus vulgaris X	128
Providencia stuartii Harding	32
Enterobacter cloacae NCTC 1005	64
Enterobacter aerogenes T660	128
Citrobacter freundii W18	128
Morganella morganii F	>1024
Serratia marcescens US9	>1024
Pseudomonas aeruginosa R3	>1024
Bacteroides fragilis BC4	>1024

Mechanism(s) of Resistance Studies

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 _____ . These authors also found that there was a significant correlation between the concentration of mupirocin required to inhibit 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. Recent studies have demonstrated that the high and low level resistant isolates have different genetic loci and mechanisms of resistance. The low level resistance is found on chromosomal genes that code for a modification of the normal isoleucine

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t-RNA synthetase so it has decreased binding for mupirocin. The genes involved in high level mupirocin resistance are found on a plasmid that also commonly encodes resistance to cadmium, mercuric chloride, propanamide isethionate and ethidium bromide. It is of interest that methicillin and mupirocin resistances are often found together in Staph isolates (see sentry survey discussed in detail below under epidemiology). The high level resistance is mediated via the acquisition of an entirely new isoleucine transfer RNA. (J. Medical Micro, 2001, volume 50, p 909-915, and Antimicrobial Agents and Chemotherapy, 2002, p. 438-442).

Epidemiological Studies (Published Literature)

As mentioned, high level resistance to mupirocin is being observed. Up until 1995 when a literature search was conducted to support a bactroban submission, high level mupirocin resistance had 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

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.

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The incidence of and interest in mupirocin resistance has changed considerably since that time as my recent literature search turned up many references, more than 50, to mupirocin resistance in Staph including information from surveys, local clinical epidemics and review articles. Mupirocin resistant isolates of Staph have been found around the globe, including United States, United Kingdom, Brazil, Saudi Arabia, Kuwait, Australia, Japan, Spain, Greece, Malaysia and New Zealand. Resistant isolates have been found in burn units, skin infections including impetigo patients, blood stream infections and peritoneal dialysis patients. In burn units in Kuwait, in 1999, 75/267 patient isolates of *S. aureus* were resistant to high levels of mupirocin and the resistance was located on transferable plasmids (*Acta Tropica* 80, 2001, p155-161). In a burn unit in Australia in 1997, 56% of

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128 patient *S. aureus* isolates had high level mupirocin resistance this is contrasted with 1992, when none of the isolates from patients in this burn unit were resistant to mupirocin! (J. Med Micro 50, 2001, 558-564). There is a definite relationship between MRSA resistance and mupirocin resistance. For example, in decubitus ulcer patients in a hospital in Tennessee, twenty five percent of patients that had MRSA also were mupirocin resistant and 42% of these patients carried high level resistance. (Infect control Hosp epidemiol, 2001, 7, p459-464).

High level mupirocin resistance is found on plasmids that commonly carry resistance to other antibiotics including methicillin, gentamycin, tetracycline, fusidic acid, erythromycin, chloramphenicol, ofloxacin and SMX/TMP.

A recent study as part of the SENTRY Antimicrobial Surveillance Program (2,000) monitored mupirocin resistance rates among staphylococcal isolates. (Diag Microbiol Infect Dis 2002, 42, 283-290). The authors stated that, "the effectiveness of Mupirocin is being compromised by emerging resistance" Results of the survey detected mupirocin resistant isolates of *S. aureus* and CONS in 19/29 US medical centers, 4/5 Canadian , 3/9 Latin American and 7/18 European. The authors suggested local surveillance for mupirocin resistance, especially in the US and Canada.

The authors' table one (Microbiology Reviewers Table 3) below indicates the relationship between Methicillin resistance and Mupirocin resistance, the higher rate of mupirocin resistance in CONS versus *S. aureus* and the geographic distribution of Mupirocin resistance. For *S. aureus*, mupirocin resistance rates ranged from 0 to 1.9% in oxacillin susceptible isolates and from 4.6% to 17% in oxacillin-resistant isolates. Mupirocin resistance was much higher in CONS isolates, 5.9 to 6.7% in oxacillin susceptible isolates and 14.0 to 43.1% in oxacillin resistant isolates. Resistance to Mupirocin is widely distributed, being found in Europe, Latin and North America. *S. aureus* Mupirocin resistance rates were lower in Latin America compared to Europe and the U.S.

Table 3

Table 1
Distribution of mupirocin-resistant (MIC, ≥ 16 $\mu\text{g}/\text{mL}$) strains and resistance rates among 2,776 staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000)

Region	<i>S. aureus</i>		CoNS*	
	Oxacillin ^S (1,345)	Oxacillin ^R (814)	Oxacillin ^S (130)	Oxacillin ^R (487)
Europe	1.9	17.8	6.7	14.0
Latin America	0.0	4.6	5.9	33.7
North America	1.5	14.1	6.0	43.1
Total	1.3	13.8	6.2	32.4

* CoNS = coagulase-negative staphylococci.

Oxacillin^S = oxacillin-susceptible (MIC, ≤ 2 $\mu\text{g}/\text{mL}$ [*S. aureus*] or ≤ 0.25 $\mu\text{g}/\text{mL}$ [CoNS])

Oxacillin^R = oxacillin-resistant (MIC, ≥ 4 $\mu\text{g}/\text{mL}$ [*S. aureus*] or ≥ 0.5 $\mu\text{g}/\text{mL}$ [CoNS]) per NCCLS [2002].

Distribution of Mupirocin resistant *S. aureus* isolates is shown by site of infection in Table 4 below from the sentry (2000) survey. As can be seen, the percentage of resistant organisms varied by site and geographic region. Concerning skin isolates, the numbers of mupirocin resistant isolates per hospital center from all regions varied from 0 to 33.3%. In the U.S. the frequency of Mupirocin resistant *S. aureus* varied from 0 to 8.1%. Table 3 (Microbiology Reviewers Table 5) from the sentry survey shows the numbers of Mupirocin resistant patient isolates of CONS. These numbers are much greater, ranging from 0-100% at U.S. medical centers with an average of 38.8%. It is of interest that levels of CONS were highest in the U.S. and lower in the other countries, Canada, 0-14.3 with an average of 24.1%, Europe 0-64% with an average of 12.7% and Latin America, 0-100% with an average of 29.2%. These high levels of resistant organisms including 100% for skin infections in the U.S. lead to the conclusion that Mupirocin should not be considered for treatment of CONS and therefore, CONS should not be included in list number 2 in the label.

Table 4.

Mupirocin resistance rates among *Staphylococcus aureus* isolates listed by geographic region and site of infection^a

Region	No of centers	Objective ^a (no. tested)	% mupirocin-resistant	
			Average	Range ^b
United States	24	A (625)	5.6	0.0-17.1
		C (594)	8.2	0.0-30.2
		D (58)	5.2	0.0-8.1
		E (8)	12.5	0.0-100.0
		Total (1,285)	6.8	0.0-100.0
Canada	4	A (96)	4.2	0.0-13.3
		C (101)	3.9	0.0-14.3
		D (14)	7.0	7.0
		Total (211)	4.3	0.0-14.3
Latin America	9	A (154)	1.9	0.0-5.6
		C (11)	0.0	0.0
		D (140)	0.7	0.0-4.2
		E (9)	0.0	0.0
		Total (314)	1.3	0.0-5.6
Europe	18	A (170)	3.5	0.0-9.1
		C (169)	14.1 ^b	0.0-64.2
		D (13)	6.7	0.0-33.3
		E (1)	0.0	0.0
		Total (353)	8.7 ^b	0.0-64.2

^a SENTRY Program objectives: A, blood stream infections; C, pneumonia in hospitalized patients; D, skin and soft tissue infections; E, urinary tract infections.

^b High resistance rate heavily influenced by one epidemic cluster (see Figure 1). Range among monitored medical centers.

Table 5

Table 3
Mupirocin resistance among CoNS isolates listed by geographic region
and site of infection^a

Region	No of centers	Objective ^a (no. tested)	% mupirocin-resistant	
			Average	Range
United States	22	A (233)	39.9	0.0-52.4
		C (10)	16.7	0.0-50.0
		D (2)	100.0	100.0
		E (7)	33.3	25.0-50.0
		Total (252)	38.8	0.0-100.0
Canada	5	A (63)	28.5	20.0-41.2
		C (4)	0.0	0.0
		D (8)	12.5	12.5
		E (4)	0.0	0.0
		Total (79)	24.1	0.0-41.2
Latin America	8	A (75)	28.0	0.0-100.0
		C (1)	100.0	100.0
		D (24)	37.5	0.0-80.0
		E (6)	0.0	0.0
		Total (106)	29.2	0.0-100.0
Europe	15	A (171)	12.2	0.0-66.7
		C (7)	14.3	0.0-50.0
		D (2)	50.0	50.0
		Total (180)	12.7	0.0-66.7

^a SENTRY Program objectives: A, blood stream infections; C, pneumonia in hospitalized patients; D, skin and soft tissue infections; E, urinary tract infections.

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In vivo

Pre-clinical human and animal model studies:

Partial thickness wound infections in Swine:

Two studies were conducted in swine (by the applicant), the first study compared Mupirocin Ointment to Bactroban and Placebo while the second study compared Mupirocin to fucidic acid ointment, fucidic acid cream, Bactroban, placebo and air exposure. Thirty-six partial thickness wounds were made on each animal and each one was inoculated with *S. aureus*, 6.68 log CFU/ml, with 6 wounds being assigned per treatment group. Two wounds per treatment group were assessed at 24, 72, and 120 hours. Each wound received 0.2 ml (0.30 grams of product per dose-enough to completely cover the wound). Two wounds were cultured per experimental group at each time period and counts determined using the spiral plating system..

In the first experiment, CP-001, Mupirocin was dosed at a frequency of 1, 2 or three times per day while bactroban and placebo were dosed at 3 times per day. Results shown below in the applicant's tables 7-4 and 7-5 are somewhat confusing. In table 7-4 (Microbiology Reviewers Table 6), it is shown that Bactroban and the test ointments were equivalent in lowering *S. aureus* bacterial counts to zero. Of interest is the fact that placebo reduced counts by 4 logs as well. This reduction by placebo indicates that this model is not very good as the numbers of *S. aureus* present are now down to 2 logs or about 229 in placebo, organism numbers reduced from 4.8 million organisms. This difference of 229 versus zero might be statistically significant but in all probability not biologically. The applicant indicated that it was a good thing that counts had gone up for all bacteria, see table 7-5 (Microbiology Reviewers Table 6), indicating a return of normal flora. However, organisms were not isolated and identified to determine if this represents normal flora returning or replacement of the inoculated *S. aureus* by other pathogens.

Table 6.

Table 7-4: *Staphylococcus aureus* ATCC 6538 recovery (log CFU/mL mean \pm SE)
Initial inoculum: 6.68 log CFU/mL

TREATMENT GROUPS	ASSESSMENT TIMES (hrs)		
	24	72	120
Bactroban® Ointment (3x/day)	0.00 \pm 0.0	0.00 \pm 0.0	0.00 \pm 0.0
Test Product (1x/day)	0.00 \pm 0.0	0.00 \pm 0.0	0.00 \pm 0.0
Test Product (2x/day)	0.00 \pm 0.0	0.00 \pm 0.0	0.00 \pm 0.0
Test Product (3x/day)	0.00 \pm 0.0	0.00 \pm 0.0	0.00 \pm 0.0
Placebo (3x/day)	4.62 \pm 0.4	2.69 \pm 0.9	2.36 \pm 0.8

Table 7-5: All Bacteria including *S. aureus* (log CFU/mL mean \pm SE)
Initial inoculum: 6.68 log CFU/mL

TREATMENT GROUPS	ASSESSMENT TIMES (hrs)		
	24	72	120
Bactroban® Ointment (3x/day)	1.88 \pm 0.6	0.00 \pm 0.0	1.33 \pm 0.6
Test Product (1x/day)	3.76 \pm 0.4	1.32 \pm 0.6	3.79 \pm 0.4
Test Product (2x/day)	4.33 \pm 0.3	0.41 \pm 0.4	5.66 \pm 0.8
Test Product (3x/day)	3.97 \pm 0.5	1.03 \pm 0.7	3.80 \pm 0.5
Placebo (3x/day)	5.61 \pm 0.2	5.89 \pm 0.4	6.41 \pm 0.4

The second study in swine appears to be a better study, in that the air-exposed and placebo-treated wounds retained more *S. aureus* counts than did the antibiotic treated wounds. However in the placebo exposed wounds, 99% of the *S. aureus* were lost while 90% were lost in the Air exposed wounds at the 120 hour reading. The test compounds reduced wound counts by 100% by 120 hours (technically, not 100% as the assay limit is 1.43 logs). Concerning total bacterial counts, they were 5-fold higher in the placebo and 10 fold higher in the air exposed than in the wounds treated with test compound at 120 hours. I find the biological-medical significance of these experiments difficult to evaluate. Results of the second study are shown in the sponsor's tables 7-11 and 7-12 (Microbiology Reviews Table 7) below.

Table 7.

Table 7-12: All bacteria including *Staphylococcus aureus* ATCC 6538 (log CFU/mL mean \pm SD)

Initial Inoculum: 6.62 log CFU/mL

24 hours cultures

Fusidic Acid Ointment	Fucidin® Cream	Bactroban® Ointment	Placebo	Mupirocin Ointment, 2%	Air Exposed
6.38 \pm 0.65	4.29 \pm 0.29	3.04 \pm 0.38	6.97 \pm 0.57	3.29 \pm 0.85	6.51 \pm 0.49

72 hours cultures

Fusidic Acid Ointment	Fucidin® Cream	Bactroban® Ointment	Placebo	Mupirocin Ointment, 2%	Air Exposed
5.66 \pm 0.82	3.65 \pm 0.80	0.46 \pm 1.11	5.68 \pm 0.50	2.67 \pm 1.40	6.57 \pm 0.55

120 hours cultures

Fusidic Acid Ointment	Fucidin® Cream	Bactroban® Ointment	Placebo	Mupirocin Ointment, 2%	Air Exposed
6.68 \pm 0.93	6.71 \pm 0.27	6.75 \pm 0.18	7.35 \pm 0.07	6.64 \pm 0.02	7.57 \pm 0.12

Note - The minimal detectable value of the spiral platter is 1.43 log CFU/ml.

Study KGL#4323: Human pilot study

A human pilot study was conducted (by the applicant) to evaluate the antimicrobial effects of test product on expanded resident flora *in vivo* and the results are presented in Table 8. The resident forearm flora of 12 volunteers was expanded to 10⁵ or 10⁶ organisms per 2 square centimeters and the area treated with Mupirocin, Bactroban, untreated or vehicle. Results of the total aerobic counts are shown in table 7-2 below. Bactroban or Mupirocin ointment resulted in a 99% reduction in aerobic counts after 24 hours while untreated and placebo resulted in no reduction. Although not shown, the dominant organisms were staphylococci, sensitive to mupirocin and they were greatly reduced. In subjects with micrococci and aerobic diphtheroids as the dominant organisms their counts were not reduced to the same extent as patients whose skin flora was staph dominant. The interpretation of this experiment is that Mupirocin was equivalent to Bactroban in the eradication of susceptible bacterial strains that are part of an expanded resident flora including commensal *S. aureus* isolates. It also indicates that this new formulation of Mupirocin is effective in eradicating Staph organisms on the surface of the skin.

Table 8.

Table 7-2: Total Aerobes log/ cm²

Subject Number	Control	A	B	C	D
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
N	11	11	11	11	11
AVERAGE	6.74	4.59	4.45	4.18	6.36
Log					
S.D.	0.91	1.24	1.16	2.12	0.45

- A: Bactroban[®] Ointment (Mupirocin Ointment, 2%)
- B: Mupirocin Ointment, 2% Batch No.: M01C101
- C: Mupirocin Ointment, 2% Batch No.: M01B103
- D: Mupirocin Ointment, 2% - Placebo Batch No.: M01V118

**APPEARS THIS WAY
ON ORIGINAL**

Pharmacokinetics: Pharmacokinetics was not presented in the microbiology portion of the submission and will not be included in this review. The submission to the PK reviewer indicates that systemic exposure to Mupirocin from this formulation is minimal. Since mupirocin is rapidly converted to an inactive form when it reaches human systemic circulation, it will have no effect on the resident microbial flora within the human body and therefore is not of clinical microbiological concern.

CLINICAL EFFICACY:

One clinical study was carried out by the applicant with his new formulation of Mupirocin. The study designated as CPL-002 was titled, "A Multicenter, double-Blind Study Comparing Clay-Park LABS, INC.'S Mupirocin Ointment, 2% and Bactroban® Ointment (Mupirocin Ointment, 2%) In The Treatment Of Impetigo." Male and female subjects were enrolled from South Africa who were 2 years of age and up while patients from Puerto Rico were age 18 months and up. Study entrants had to have a microbiologically confirmed clinical diagnosis of impetigo contagiosa or uncomplicated blistering impetigo with a presumptive identification of *Staphylococcus aureus* and/or *Streptococcus pyogenes*. Swab cultures were taken from the target lesion for bacterial isolation and identification, and the target lesion was graded according to the Skin infection Rating Scale (SIRS) and an overall clinical evaluation completed. The treatment period was 7 days and subjects returned within a 3 day window following treatment for clinical and bacteriological evaluation. The microbiological efficacy measure was bacteriological success proportions at the end of treatment visit and the follow-up visit (day 12-16). Microbiological success was the presumptive or culture negative findings for the organisms of interest, *S. pyogenes* and *S. aureus* in patients who were culture positive at study entrance. Results comparing patients treated with Mupirocin or bactroban are shown in the applicant's table 7-22 below.

As shown in Table 7-22 (Microbiology Reviewers Table 8) clinical results are equivalent for patients treated with bactroban or mupirocin ointments both for the per protocol (PP) and modified intent to treat (MITT) groups with success rates of 76-84%. Bacteriological cure rates are also equivalent for the two groups, ranging from 92-98%. It is of interest that the bacteriological response is much higher than the clinical. This indicates that other organisms besides *Staphylococcus aureus* and *Streptococcus pyogenes* could be involved in the pathology of the disease. It should be recalled that mupirocin has little activity against anaerobes, fungi or gram-negative bacteria. Previous clinical studies have indicated that failures are usually attributed to gram negative bacteria. An attempt to isolate gram- negatives or determine what organisms were present in clinical failures was not attempted in these studies. Concerning the microbiology of these studies, MICs were determined by e-test, it should be noted that there is no standard MIC testing method for Mupirocin so results can vary depending on the test methods used. The MIC values for *S. aureus* ranged from _____ with only two isolates having MICs exceeding 0.50 µg/ml. The MIC values for these two isolates exceeded 1024 µg/ml but both isolates were eradicated, they were both in the mupirocin treated group. *S. pyogenes* isolates exhibited MIC values ranging from _____

Table 8.

Table 7-22: Secondary Analysis: Clinical Response At Day 7-9 And Bacteriological Response At Day 7-9 And Day 12-16

	Mupirocin Ointment, 2%	Bactroban® Ointment	Two-Sided 95% CI for Equivalence of Mupirocin Ointment, 2% to Bactroban® Ointment
Day 7-9			
<u>Clinical Response: Per-Protocol Subjects(n,%)</u>			
	(N=233)	(N=242)	
Success	195 (84%)	190 (79%)	-2.26% to 12.62%
Failure	38 (16%)	52 (21%)	
<u>Clinical Response: Modified Intent-to-Treat Subjects(n,%)²</u>			
	(N=279)	(N=279)	
Success	224 (80%)	213 (76%)	-3.25% to 11.13%
Failure	55 (20%)	66 (24%)	
<u>Bacteriological Response: Per-Protocol Subjects(n,%)³</u>			
	(N=233)	(N=242)	
Success	232 (100%)	238 (98%)	-1.24% to 2.87%
Failure	1 (0%)	3 (1%)	
Unevaluable	0 (0%)	1 (0%)	
<u>Bacteriological Response: Modified Intent-to-Treat Subjects(n,%)²</u>			
	(N=279)	(N=279)	
Success	267 (96%)	265 (95%)	-3.14% to 4.57%
Failure	12 (4%)	14 (5%)	
Day 12-16			
<u>Bacteriological Response: Per-Protocol Subjects(n,%)</u>			
	(N=233)	(N=242)	
Success	228 (98%)	237 (98%)	-3.08% to 2.92%
Failure	5 (2%)	5 (2%)	
<u>Bacteriological Response: Modified Intent-to-Treat Subjects(n,%)²</u>			
	(N=279)	(N=279)	
Success	261 (94%)	258 (92%)	-3.51% to 5.66%
Failure	18 (6%)	21 (8%)	

¹ Confidence intervals calculated using Wald's method with Yate's continuity correction.
² A response of 'Unevaluable' was treated as a missing efficacy result, and missing efficacy results were treated as failures in the analyses.
³ Only subjects with 'Success' or 'Failure' responses were included in the calculation.

**APPEARS THIS WAY
ON ORIGINAL**

Mupirocin

Clay-Park Labs, Inc.

Concerning resistance development: In subjects where post-baseline cultures were obtained, no increase in the MIC values of the isolates was observed. There were 78 *S. aureus* isolates identified from the clinical study, three of which were resistant to methicillin. None of the 28 *S. pyogenes* clinical isolates were resistant to methicillin. (Methicillin resistance testing was conducted by oxacillin disk). It is of interest that in the Sentry survey, 38% of isolated *S. aureus* were MRSA. The *S. aureus* isolates were multi-resistant, being resistant to 9 out of 16 tested antibiotics while the *S. Pyogenes* isolates were multiresistant to 5 out of the 16 tested antibiotics. This information was provided in Table 9 below and will not be discussed in detail.

APPEARS THIS WAY
ON ORIGINAL

Susceptibility breakpoints:

Breakpoints, including MIC and zone diffusion testing are not established for antibiotics used for topical application. This is because the concentrations of antibiotic on the skin are extremely high making normal susceptibility breakpoints irrelevant. However, as stated earlier, several authors have suggested following Mupirocin MICs due to the finding of increased numbers of resistant Staph, especially following long-term usage in the hospital and nursing home environments. Although MRSA strains do not appear to be common amongst skin isolates in the applicant's study, chronic usage or off-label usage of bactroban has led to resistance development..

Joel Unowsky
Microbiology reviewer

Concurrence only:

SMicro/ASheldon
RD#1 Initialed 11/01/02 ATS
Final review initialed 11/6/02 ATS

**APPEARS THIS WAY
ON ORIGINAL**

DepDir/LGavrilovich

cc: Orig. NDA # 50-788
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon
HFD-502
HFD-520/Stat/LSue-Chi
HFD-520/MicroJUnowsky
HFD-520/MO/DBostwick

NDA 50-788
Mupirocin
Clay-Park Labs, Inc.

21 of 21

HFD-520/Pharm/AEllis
HFD-520/Chem/MSloan
HFD-520/CSO/MDillon-Parker
HFD-520/PK/CBonapace

**APPEARS THIS WAY
ON ORIGINAL**

-

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

/s/

Joel Unowsky
11/7/02 10:25:46 AM
MICROBIOLOGIST

Albert Sheldon
11/7/02 10:41:07 AM
MICROBIOLOGIST

Lillian Gavrilovich
11/20/02 11:35:44 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 1
Consult

NDA # 50-788

Date Completed: November 27, 2002

Reviewer: Albert T. Sheldon, Jr. Ph.D.

Sponsor (IND)/Applicant (NDA):
Clay-Park Labs, Inc.
1700 Bathgate Ave.
Bronx, NY 10457

Chem/Ther. Type:
Topical antibiotic

Submissions Reviewed:
November 21, 2002 facsimile.

Providing for:
A change in the proposed product label sent to the applicant during labeling negotiations.

Product Name(s):

Proprietary: Mupirocin Ointment

Non-proprietary/USAN: Mupirocin

Compendia: Mupirocin

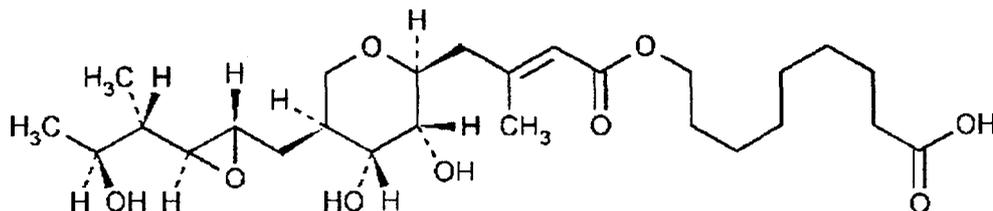
Code name/number: NA

Chemical name: Nonanoic acid, 9-[[[3-methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[[3-(2-hydroxy-1-methylpropyl)oxiranyl]methyl]-2 H-pyran-2-yl]-2-butenyl]oxy]-, [2 S-2a(E),3b,4b,5a[2 R*, 3 R*(1 R*,[2 R*)]]]-.

Mupirocin Ointment

Clay-Park Labs, Inc.

(E)-(2 S, 3 R, 4 R, 5 S)-5-[(2 S,3 S,4 S,5 S)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-b-methyl-2 H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid

Structural formula:**Molecular formula:** C₂₆H₄₄O₉**Dosage form(s):** Ointment**Route(s) of administration:** Topical**Pharmacological Category:** antimicrobial**Dispensed:** Rx X OTC **Initial Submission Dates**

Received by CDER:	March 2, 2002
Received by Reviewer:	October 4, 2002
Review Completed:	October 31, 2002

Supplements/Amendments:

Received by CDER:	November 21, 2002
Received by Reviewer:	November 21, 2002
Review Completed:	November 25, 2002

Related Documents: NA**Remarks:**

Clay-Park labs submitted, on November 21, 2002, a facsimile requesting that we consider deleting a sentence found in the microbiology section of the proposed package insert.

Mupirocin Ointment
Clay-Park Labs, Inc.

The facsimile document contains a request to delete the following sentence from line 48-49 of the proposed package insert:

"Methicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase negative staphylococci."

The applicant, in support of the deletion of this statement, submits the following rationale, and their comments are highlighted in italics for added emphasis.

1. *The statement conflicts with one in the previous paragraph indicating that "Due to the unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobials." (lines 40-41)*

Reviewer's comments: The statements are not in conflict. The definition of cross-resistance at the genetic level is a mechanism of resistance that affects the efficacy of different classes of drugs simultaneously. For example, resistance to the macrolide, lincosamide and streptogramin B class of antimicrobials is mediated by the erythromycin resistance methylase (*erm*). This resistance mechanism mediates its action by methylation of the adenine of 23S ribosomal RNA resulting in cross-resistance to the three antibiotic drug classes. Thus, the *erm* gene mediates resistance to three classes of antibiotics.

The fact that an organism carries resistance to multiple and unrelated antibiotics does not characterize it as cross-resistant to antibiotics. It characterizes the microorganism as multiple resistant to various antibiotics.

The statement that we provide in the mupirocin product label does not suggest that resistance to mupirocin results in cross-resistance to Methicillin or visa versa. What we do say is that both resistance mechanisms appear to be found together frequently in staphylococcal species. This frequency range is discussed below in comment 3.

2. *This statement is not supported by the data submitted in Clay-Park Labs, Inc.'s NDA, nor do we believe that the literature reference provided by Clay-Park Labs, Inc support such a statement.*

Reviewers comments: The applicant appears to be under the mistaken and naive assumption that the FDA can only use data presented in the sponsor submission in the assessment of the products safety, efficacy, or development of the product label. They imply that we should only use the data submitted in their submission for our assessment. Since no data was

submitted by Clay-Park Labs, Inc. to address the points of our proposed sentence, then we should delete the sentence.

The fact of the matter is that the agency can use any scientifically valid data to determine the safety, efficacy, and labeling of a product. If published literature exists in the public domain that addresses issues not addressed by the sponsor, it is appropriate for the agency to use this information in the assessment of the product or the development of the product label. This is what the agency has done to assure a fair assessment of the product.

- 3 *Based on FDA's comments during the pre-NDA meeting (held on September 5, 2001), it was Clay-Park Labs, Inc. understanding that no reference should be made to,*

Reviewers comments: According to the agencies minutes of the Pre-NDA meeting, the applicant of _____ Caly-Park, Labs, was advised that "with regards to the Microbiology section of the labeling, data will need to be provided in order to support the statements regarding _____ in the labeling. CPL stated that they would remove the statement in the labeling unless there was data to support its inclusion....In general, the FDA stated that unless CPL can demonstrate that _____ is a pathogen in the indication impetigo, then _____ cannot be included in the labeling."

It is clear from the previous material from the agencies minutes and additional details provided within that document, that we had concern regarding the inclusion of _____ in the product label for several reasons. One reason include that published scientific literature is now available in the public domain that suggests that _____ are began to emerge that are also resistant to mupirocin. Prior to 1995, the published evidence was minimal in that few publications adressed mupiroci resistance in _____. Since then, more than 50 papers have been published that address the emergence of resistance in _____ and coagualse negative staphylococci. For example, the Sentry Antimicrobial Surveillance Program assessed the mupirocin resistance rates in 2,779 staphylococcal isoaltes obtained from four regions of the world (Table 1).¹ The are several conncusions that can be drawn from this table.

- The first is that the rate of mupirocin resistance is more closely associated with oxacillin (methicillin) resistant staphylococcal strains than oxacillin susceptible strains. Mupirocin resistance in staphylococci is approximately 14.5% in methicillin resistant strains and 1.5% in MSSA strains in the United States. That is, mupirocin resistance is 10-fold higher in methicillin resistant strains than in MSSA strains. In coagulase-negative staphylococci, the same trend is noted; mupirocin resistance is higher in MRCoNS (43.1%) than in MSCoNS (6.0%). The rate of mupirocin resistance is 7.2 fold greater in methicillin resistant coagulase-negative staphylococci than in susceptible strains. This evidence clearly support the notion that there is more mupirocin resistance in methicillin resistant and MRCoNS than in sensitive strains. This is an expected result since Bactroban is approved for prophylaxis of methicillin resistant nasal carriage in health care professionals. It is this use that has driven the emergence of mupirocin resistance in methicillin resistant strains.
- The second observation that can be made from Table 1 is that the coagulase negative staphylococci (CoNS) are more likely to be mupirocin resistant than are *S. aureus*.

We believe that the sentence as proposed is supportable by the scientific evidence that the prevalence of mupirocin resistance is greater in methicillin resistant strains than in methicillin susceptible strains. These observation do not imply that there is cross-resistance between mupirocin and methicillin.

Table 1
Distribution of mupirocin-resistant (MIC, $\geq 16 \mu\text{g/mL}$) strains and resistance rates among 2,776 staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000)

Region	<i>S. aureus</i>		CoNS ^a	
	Oxacillin ^S (1,345)	Oxacillin ^R (314)	Oxacillin ^S (130)	Oxacillin ^R (487)
Europe	1.9	17.8	6.7	14.0
Latin America	0.0	4.6	5.9	33.7
North America	1.5	14.1	6.0	43.1
Total	1.3	13.8	6.2	32.4

^a CoNS = coagulase-negative staphylococci.

Oxacillin^S = oxacillin-susceptible (MIC, $\leq 2 \mu\text{g/mL}$ [*S. aureus*] or $\leq 0.25 \mu\text{g/mL}$ [CoNS])

Oxacillin^R = oxacillin-resistant (MIC, $\geq 4 \mu\text{g/mL}$ [*S. aureus*] or $\geq 0.5 \mu\text{g/mL}$ [CoNS]) per NCCLS [2002].

Conclusions/Recommendations:

The statement proposed by the agency, "Methicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase negative staphylococci" is supportable by the published literature. It is possible that we could modify the statement to reflect the rates of resistance as described in the reference but there is concern that these mupirocin resistance rates will be increasing with time. Thus, we would recommend that we keep the existing sentence.

Albert T. Sheldon, Jr. Ph.D.
Microbiology Team Leader

Cc: Original NDA No. 050-788
Microbiologist, HFD-520
File name: N50788#3.doc

SMicro/ATSheldon

DepDir/LGavrilovich

¹ Deshpande, LM, AM Fix, and MA Pfaller (2002) Emerging elevated mupirocin resistance rates among staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000): correlations of results from disk diffusion, Etest and reference dilution. *Diagnostic Microbiology & Infectious Disease*. 42:283-290.

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

/s/

Albert Sheldon
11/27/02 10:26:50 AM
MICROBIOLOGIST

Lillian Gavrilovich
11/29/02 03:20:03 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

NDA 50-788 (addendum)
Mupirocin
Clay-Park Labs, Inc.

1 of 3

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review
Addendum

NDA # 50-788

DATE COMPLETED: October 31, 2002

APPLICANT:

Clay-Park Labs, Inc.
1700 Bathgate Ave.
Bronx, NY 10457

CHEM/THER. TYPE: Topical Antibiotic

SUBMISSION REVIEWED:

PROVIDING FOR: Clinical and Microbiological Studies in support of labeling claims for topical treatment of impetigo caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.

PRODUCT NAME:

Proprietary: Mupirocin Ointment , 2%

Non-Proprietary/USAN:

CHEMICAL NAME, MOLECULAR FORMULA, MOL. WT.

Chemical Name: (E)-(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihoxypyran-2-yl]-3-methylbut-2-enoyloxy]nonanoate

Molecular Formula: C₅₂H₈₆O₁₈

Molecular Weight: 500.63

DOSAGE FORM: Cream containing castor oil

STRENGTH: 2%

ROUTE OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Antiinfective

DISPENSED: Rx

INITIAL SUBMISSION:

Received by CDER: 3/7/02

Received by Reviewer: 10/4/02

NDA 50-788 (addendum)
Mupirocin
Clay-Park Labs, Inc.

3 of 3

Joel Unowsky
Microbiology reviewer

Concurrence only:

SMicro/ASheldon
RD and Final initialed 11/13/02 ATS

DepDir/LGavrilovich

cc: Orig. NDA # 50-788
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon
HFD-502
HFD-520/Stat/LSue-Chi
HFD-520/MicroJUnowsky
HFD-520/MO/DBostwick
HFD-520/Pharm/AEllis
HFD-520/Chem/MSloan
HFD-520/CSO/MDillon-Parker
HFD-520/PK/CBonapace

SEE CLINICAL
REVIEW

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 50-788 Supplement Type (e.g. SE5): None Supplement Number: None

Stamp Date: February 8, 2002 Action Date: _____

HFD 520 Trade and generic names/dosage form: Mupirocin Ointment, 2%

Applicant: Clay - Park Labs, Inc Therapeutic Class: 3-S

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Impetigo

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. <u><2</u>	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

APPEARS THIS WAY
ON ORIGINAL