

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 50-746**

**MEDICAL REVIEW(S)**

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CLINICAL REVIEW OF NDA 50-746

Original Submission

Date of Submission: December 12, 1996

Date CDER Received: December 12, 1996

Date Assigned to Reviewer: December 16, 1996

Date Review Completed: September 22, 1997

Date Review to Supervisor: October 10, 1997

Drug: Bactroban® Cream 2% (mupirocin calcium cream).

Applicant: SmithKline Beecham Pharmaceuticals, Philadelphia, PA 19101.

Related IND: IND

Proposed Indication: "Bactroban Cream (mupirocin calcium cream), 2% is indicated for the treatment of secondarily infected traumatic skin lesions due to *Staphylococcus aureus*, beta-hemolytic *Streptococcus*, and *Streptococcus pyogenes*."

Proposed Dosage and Administration: "A small amount of Bactroban Cream should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated."

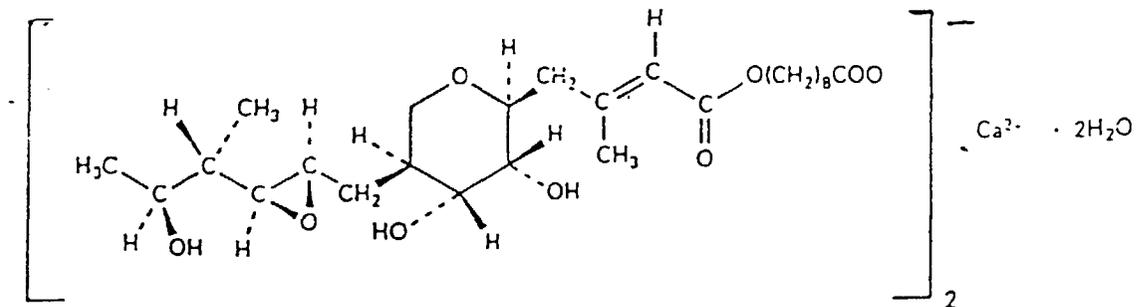
Packaging: This product is to be supplied in 15 g and 30 g tubes.

Formulation:

Component	Composition % w/w
✓ Mupirocin calcium (micronized)	2.15*
✓ Mineral oil, USP	
✓ Cetomacrogol 1000, BP	
✓ Stearyl alcohol, NF	
✓ Cetyl alcohol, NF	
✓ Benzyl alcohol, NF	
✓ Phenoxyethanol, BP	
✓ Xanthan gum, NF	
✓ Purified water, USP	

\*Equivalent to 2.0% mupirocin free acid. Actual amount will be based on individual batch potency. The overage which will be allowed in formulating the product has not been determined.

The structural formula of mupirocin calcium is as follows:



Molecular formula -  $(C_{52}H_{86}O_{18})_2 Ca \cdot 2 H_2O$

Molecular weight - 1075.3

#### Related NDA's:

1. NDA 50-591, Bactroban Ointment 2% (mupirocin ointment). This NDA was approved on December 31, 1987. The approved indication reads as follows:

Bactroban (mupirocin) Ointment is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus*, beta-hemolytic *Streptococcus*,\* and *Streptococcus pyogenes*.

\*Efficacy for this organism in this organ system was studied in fewer than ten infections.

2. NDA 50-703, Bactroban Nasal 2% (mupirocin calcium ointment). This NDA was approved on September 18, 1995. The approved indication reads as follows:

Bactroban<sup>®</sup> Nasal (mupirocin calcium ointment), 2% is indicated for the eradication of nasal colonization with methicillin-resistant *Staphylococcus aureus* in adult patients and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant *S. aureus* infection during institutional outbreaks of infections with this pathogen.

**Background:** Mupirocin is a naturally occurring antibiotic which has a unique chemical structure not seen in other antibacterial agents. Resistance to mupirocin has been slow to develop, although there have been some recent publications concerning resistance to this drug by *S. aureus* (Ramsey, M., Bradey, F., Kauffman, C., and Morton, T., 1996. Identification of chromosomal location of *Mup A* Gene, Encoding Low-Level Mupirocin Resistance in Staphylococcal Isolates. *Antimicrob Agents Chemother* 40:2820-2823.)

Mupirocin has demonstrated excellent effectiveness to date against many aerobic Gram-positive bacteria, including *S. aureus*, *Staphylococcus epidermidis*, *-Streptococcus pyogenes* and other  $\beta$ -hemolytic streptococci. Bactroban ointment (NDA 50-591) has become a recognized treatment for impetigo throughout the world, and has been approved in 103 foreign countries. In 1989, SmithKline submitted an efficacy supplement requesting the approval of Bactroban for the treatment of secondarily infected traumatic lesions of the skin. In 1990, this supplement was amended to

request approval for the treatment of

This supplement was made in 1993 because the results were inconsistent between investigators and studies (i.e., some investigators found the product to be greatly superior to the vehicle, while other investigators found no differences between the groups).

Bactroban Ointment (NDA 50-591) was investigated overseas as a treatment for *S. aureus* colonization of the nares. Although the treatment was successful, the formula caused unacceptable irritation of the nasal mucosa. Therefore, the more stable calcium salt was formulated for intranasal use. In addition to the U.S., Bactroban Nasal Ointment (NDA 50-703) has been approved in 21 foreign countries, including the United Kingdom and Switzerland.

Bactroban Cream has not been approved anywhere. When IND was first submitted, the applicant planned two pivotal clinical studies: one in secondarily infected traumatic skin lesions

They were informed that two studies would be required for the approval of either indication, and subsequently elected to concentrate on the skin lesion indication first.

The following is a quote from the "Microbiology" subsection of the proposed package insert (the language is identical to that used in the approved Bactroban Nasal insert):

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain Gram-negative bacteria as well. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no *in vitro*-cross resistance with other classes of antimicrobial agents.

Resistance occurs rarely, however, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC>1024 mcg/mL) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved locally by topical application. Mupirocin exhibits *in vitro* MICs of 4 mcg/mL or less against most (>90%) strains of *Staphylococcus aureus*, beta-hemolytic *Streptococcus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Streptococcus pyogenes*. The clinical significance of the *in vitro* activity against *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* is unknown.

**Material Reviewed:** The applicant has submitted the following materials concerning testing in humans in support of the NDA:

A. Clinical Efficacy Studies in Infected Traumatic Lesions

<u>Study No.</u>	<u>Pivotal Studies</u>	
	<u>Design</u>	<u>No. Subjects</u>
4910 F/129 A	Double-blind, double-dummy	141 Mupirocin
	Parallel-group	150 Cephalixin
	active control	

4910 F/129 B	Double-blind, double-dummy	176 Mupirocin
	Parallel-group	163 Cephalexin
	active control	

## B. Clinical Efficacy Study in Infected Eczema

Supportive Study

<u>Study No.</u>	<u>Design</u>	<u>No. Subjects</u>
4910 F/130	Double-blind, double-dummy	69 Mupirocin
	Parallel-group,	56 Cephalexin
	active control	

## C. Human Pharmacokinetics (Absorption)

<u>Study No.</u>	<u>Design</u>	<u>No. Subjects</u>
4910 F/142	Open	19 adults, 10 children

## D. Skin Irritation and Sensitization

<u>Study No.</u>	<u>Design</u>	<u>No. Subjects</u>
4910 F/109	Paired comparison, placebo control	102

Reviewer's Comment: The applicant has also submitted, by reference, studies performed using other mupirocin formulations concerning absorption through human skin. These studies were described as part of the review of NDA 50-703 and will not be further dealt with in this review.

In addition, dermal irritancy and sensitization studies were performed with an alternate Bactroban Cream formulation which was not developed. These studies will not be described in this review.

Finally, the human absorption study (4910 F/142) is referred to by the applicant as containing information on the local and systemic tolerance to Bactroban Cream. Therefore, the clinical reviewers will describe these tolerance data. The reader is referred to FDA's biopharmaceutics review for a critical analysis of the absorption data.

This review will consist of the following sections:

- I. Review of Clinical Efficacy Studies (Pivotal and Supportive) and Efficacy Summary

II. Review of Safety Studies (Absorption, Irritancy and Sensitization) and Safety Summary

III. Review of Labeling

IV. Conclusions and Recommendations

Other Reviews:

1. Pharmacology/toxicology: In her review dated January 10, 1997, Dr. Terry Peters reached the following conclusion:

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.

2. Microbiology: In his review dated July 2, 1997, Dr. James King made the following labeling recommendations:

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

3. Biopharmaceutics: In her review dated April 1, 1997, Dr. Funmilayo Ajayi had the following comments:

GENERAL COMMENTS (Need not be sent to Firm):

1. The systemic availability of mupirocin following topical application of the ointment and nasal ointment was demonstrated 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. Chemistry: This review is not yet available.
5. Statistics: In her review dated May 25, 1997, Dr. B. Sue Bell had the following comments:

LABELING

Conclusion:

In the treatment of secondarily infected open wounds such as small lacerations, sutured wounds, or abrasions, mupirocin calcium cream applied topically three times daily for ten days meets DAIDP's guidelines for establishing therapeutic equivalence to cephalexin administered orally four times a day.

**I. Review of Clinical Efficacy Studies (Pivotal and Supportive) and Efficacy Summary**

- A. Study Title: A Comparative Study of the Safety and Efficacy of Mupirocin Calcium Cream with Cephalexin in the Treatment of Secondarily Infected Open Wounds (Study No. BRL 4910 F/129 A).

Investigators: This was a multi-center study conducted at 26 independent sites under a common protocol. The following presentation lists the clinical investigators and the intent-to-treat patient enrollment for each treatment arm. The presentation also includes the numbers of patients who were clinically (CLIN) evaluable per protocol at follow-up and bacteriologically (BACT) evaluable per protocol at the follow-up visit (Mup = Bactroban; Ceph = Cephalexin). The CV's for the investigators have been reviewed and found acceptable.

Study Center/Number/ Investigator/ Location	ITT		CLIN		BACT	
	MUP	CEPH	MUP	CEPH	MUP	CEPH
005 Jean Chin, M.D. Garth Russo, M.D. Univ. Health Service Athens, GA	6	8	3	5	0	2
007 Zorba Paster, M.D. Dean Medical Center Oregon, WI	15	16	13	13	1	2
008 Robert Charles, M.D. Department of Dermatology Petoskey, MI	1	1	0	0	0	0
011 Robert Fiddes, M.D. 12291 E. Washington Blvd. Whittier, CA	18	22	12	18	6	10
012 Virginia Sulica, M.D. Georgetown University Medical Center Washington, DC	10	12	8	8	3	3
013 Richard Tucker, M.D. Wenatchee Valley Clinic Wenatchee, WA	6	4	6	2	3	1
015 Michael Maloney, M.D. Cherry Creek Dermatology Denver, CO	2	2	0	2	0	1
019 Dennis McCluskey, M.D. Clinical Resources Mogadore, OH	2	3	2	2	1	2
020 Scott Touger, M.D. Kumjad Unnopet, M.D. Hill Top Research Homewood, AL	2	2	1	1	0	1
023 Toivo Rist, M.D. Dermatology Associates Knoxville, TN	2	1	2	0	0	0
024 Raymond Tidman, M.D. Burns Professional Bldg. Blue Ridge, GA	2	2	1	0	0	0
026 Thomas Garland, Jr., M.D. Garland & Associates Lawrenceville, NJ	1	3	1	2	1	1
028 Lawrence Parish, M.D. Paddington Testing Co., Inc. Philadelphia, PA	5	5	4	4	2	3
031 Frank Nieto, Jr., MD 1330 Rockefeller Ave Everett, WA	2	0	0	0	0	0

Study Center Number/ Investigator/Location	ITT		CLIN		BACT	
	MUP	CEPH	MUP	CEPH	MUP	CEPH
033 Arthur Balin, M.D. 2129 Providence Ave. Chester, PA	11	13	9	8	2	5
036 Lawrence Eron, M.D. Kauai Medical Group Lihue, HI	13	11	7	7	6	2
037 Stephen Kraus, M.D. 3003 Rivermeade Drive Atlanta, GA	30	27	22	18	9	10
038 Seymour Bross, M.D. Sunnyvale Clinic Sunnyvale, CA	2	1	1	0	0	0
046 Lloyd Cleaver, D.O. 700 W. Jefferson Street Kirlasville, MO	1	0	0	0	0	0
047 James Dynan, M.D. Lansdale Medical Group Lansdale, PA	0	1	0	1	0	1
051 Frank Maggiacomo, DO Silver Lake Medical, Inc. Providence, RI	4	5	3	2	1	1
054 Larry Gilderman, D.O. University Clinical Research Assoc. Pembroke Pines, FL	2	1	2	1	1	1
056 Barry Miskin, M.D. Palm Beach Research Center West Palm Beach, FL	6	7	3	5	1	2
064 Thomas Jefferson, MD Little Rock Children's Clinic Little Rock, AR	3	7	2	6	1	4
067 Charles Sheaffer, MD Kathleen Salter, MD Chapel Hill Peds Chapel Hill, NC	2	1	0	0	0	0
068 William Parker, M.D. Highland Clinic Shreveport, LA	14	16	13	14	9	5
<b>TOTAL</b>	<b>162</b>	<b>171</b>	<b>115</b>	<b>119</b>	<b>47</b>	<b>57</b>

Study Dates: August 31, 1994 - April 19, 1996

Study Objectives: The following is taken directly from volume 20, p. 4 of the NDA:

**Primary:** To compare the efficacy, safety and tolerance of mupirocin calcium cream with oral cephalexin in the treatment of patients with a secondarily infected open wound, such as a small laceration, sutured wound, or abrasion.

**Secondary:** To pharmaco-economically compare the direct medical resources utilized in the treatment of patients with a secondarily infected open wound, such as a small laceration, sutured wound, or abrasion.

Method:

1. Study design: This was a multicenter, randomized, double-blind, double-dummy parallel-group comparison of the safety and effectiveness of Bactroban Cream and cephalexin capsules (in patients weighing >40 kg) or cephalexin suspension (in patients weighing ≤40 kg) in secondarily infected wounds. A total of 333 patients were randomized to receive study medication (162 Bactroban, 171 cephalexin).

2. Inclusion criteria: The following is taken directly from volume 20, pp. 25-26 of the NDA:

A patient was included in the study, if the patient:

- or parent/legal guardian was willing to comply with the protocol.

Note: Prior to the 12 February 1995 protocol amendment (PIDs < 800) enrollment was restricted to patients 8 years of age or older weighing more than 40 kg.

- had a secondarily infected open wound such as a small laceration, sutured wound or abrasion. A laceration or sutured wound should not have exceeded 10 cm in length with surrounding erythema not more than 2 cm from the edge of the lesion. Abrasions should not have exceeded 100 sq. cm in total area with surrounding erythema not more than 2 cm from the edge of the abrasion.

- had a positive Wright stain for WBCs.

Note: Patients enrolled prior to the 17 April 1995 protocol amendment had a Gram stain of the wound exudate performed by the central lab. Confirmation of white blood cells was based on the Gram stain result and was not a study entry criterion.

- had a Skin Infection Rating Scale (SIRS) score of at least 8 (see Appendix F of the study protocol, Appendix A herein).
- had provided written informed consent. Patients under 18 years of age must have had written informed consent from a parent or legal guardian.
- had a negative urine pregnancy test result, if female of child-bearing potential.

3. Exclusion criteria: The following is taken directly from volume 20, pp. 26-27 of the NDA:

A patient was to be excluded from the study, if the patient:

- had demonstrated a previous hypersensitivity reaction to penicillins, cephalosporins, or other  $\beta$ -lactam antibiotics, or mupirocin or any component of the drug.
- had a bacterial skin infection which, due to depth or severity, could not be appropriately treated by a topical antibiotic (e.g., cellulitis, abscess, ulcers, furunculosis).
- had a secondarily infected animal/human or insect bite, or a puncture wound.
- had systemic signs and symptoms of infection (such as fever; defined as an oral temperature greater than 101°F or 38.3°C).
- required surgical intervention for treatment of the infection prior to enrollment in the study.

Note: The preceding three exclusion criteria were not in place prior to the 17 April 1995 protocol amendment. However, these criteria were applied uniformly to all patients for the purpose of determining per protocol evaluability.

- had received a systemic antibacterial or steroid, or had applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the wound, or used soap containing an antibacterial agent within 24 hours prior to entering the study.
- had a serious underlying disease.
- was pregnant, breast feeding or planning a pregnancy during the study.
- had used an investigational drug within 30 days prior to entering the study.
- had been previously enrolled in this study.

4. Dosage and duration of therapy: In order to assure the blinding of the study, a "double-dummy" design was used. Patients received either calcium mupirocin cream 2% (Bactroban) applied 3 times daily plus a placebo for oral cephalexin 4 times daily, or oral cephalexin 4 times daily plus a placebo for Bactroban cream applied 3 times daily.

Prior to February, 1995, only patients 8 years of age or older who weighed more than 40 kg were enrolled. This was because there was no placebo for the oral suspension available. Therefore, all patients enrolled prior to February 1995, who were in the cephalexin arm, received 250 mg cephalexin capsules. Once the placebo suspension became available, children less than 8 years old or weighing less than 40 kg could be entered into the study. These patients, who were in the cephalexin arm, received an oral suspension of 125 mg Cephalexin per 5 mL dosed on a weight basis.

The treatments continued for 10 days, even if the lesion was fully healed. If the lesion failed to respond, the investigator had the option of discontinuing the patient. A patient must have received at least 3 days of therapy to be considered evaluable.

Patient evaluations were made at baseline, at day 3-5 of therapy, post therapy (2-3 days after the last dose of medication) and at follow-up (7-12 days after the last dose of medication).

Drug application/dosing was done by the patient or guardian (this was an outpatient study), according to instructions by the investigator. For the topical application of the study drug, the patient/guardian was instructed to clean the wound with warm water and a non-antibacterial soap prior to applying the medication/placebo with a sterile swab.

The use of a gauze or bandage was permitted. Use of all other topical agents was prohibited during therapy and for 7 days after therapy or until the follow-up evaluation.

5. Effectiveness parameters: As agreed to by SmithKline and HFD-520 reviewers, the primary effectiveness parameter in this study was **clinical response at follow-up** (7-12 days post therapy). The clinical response was evaluated as follows at that visit (volume 20, p. 38):

- **Persistent Clinical Success**: Complete resolution or sustained improvement of signs and symptoms of infection for those patients who were clinical successes at the end of therapy. No exudate/pus was present and no additional antibiotic therapy was required at the follow-up visit, nor was taken between the end of therapy and follow-up visits.
- **Clinical Recurrence**: Reappearance or worsening of signs and symptoms of infection for those patients who were a Clinical Success at the end of therapy, and additional antibiotic therapy was required.
- **Unable to Determine**: A valid assessment of clinical outcome could not be made (e.g., patient did not attend or consent to clinical examination; an alternate antibiotic was administered for an intercurrent illness, etc.)

Clinical efficacy assessments were performed at follow-up only for those patients who were successes at the end of therapy. Clinical failures during therapy or at the end of therapy were carried forward as clinical failures at follow-up.

There were three secondary efficacy parameters evaluated, as follows:

- a. **Bacteriological response at follow-up**. The bacteriological response to therapy at the follow-up visit (7-12 days post-therapy) was classified according to the following definitions (volume 20, p. 36):

- **Persistent Presumed Eradication**: Symptomatic response was success and a culture was not clinically indicated (based on resolution of signs and symptoms of infection).
- **Reinfection**: Eradication of pre-therapy pathogen(s) at the end of therapy, but with the appearance of one or more pathogens (not present at pre-therapy) during the follow-up period.
- **Relapse**: Initial pathogen eliminated at the end of therapy, but re-emerging during the follow-up period.
- **Unable to Determine**: Bacteriological evaluation could not be made.

A bacteriological treatment success was graded as "Persistent Presumed Eradication" at follow-up. Bacteriological failures during therapy or at end of therapy were carried forward as bacteriological failures at follow-up. Bacteriological evaluation was not done at the first treatment visit (day 3-5 of therapy) unless the patient had failed by that time.

b. **Clinical response at end of therapy.** The clinical response at the end of therapy was classified according to the following definitions (volume 20, p. 37):

- **Clinical Success:** Complete resolution of signs and symptoms of infection, or incomplete resolution of signs and symptoms of infection with no exudate/pus present, and no additional antibiotic therapy was required.

**Note:** A patient evaluated as a Clinical Success by the investigators but who had exudate present or was continued on antimicrobial therapy was changed by the sponsor to an evaluation of Unable to Determine.

- **Clinical Failure:** Inability to clear or improve the presenting signs and symptoms after three or more days of therapy and additional antibiotic therapy was required.
- **Unable to Determine:** A valid assessment of clinical outcome could not be made (e.g., patient did not attend or consent to clinical examination; an alternate antibiotic was administered for an intercurrent illness, etc.)

c. **Bacteriological response at end of therapy.** This parameter was evaluated as follows (volume 20, p. 37):

- **Presumed Eradication:** Symptomatic response was success and a repeat culture was not clinically indicated (based on resolution of signs and symptoms of infection).
- **Superinfection:** Pre-therapy pathogen(s) was eliminated but a different pathogen was isolated at end of therapy.
- **Failure:** Non-eradication of initial pathogen.
- **Unable to Determine:** Bacteriological evaluation could not be made.

The signs and symptoms of infection were evaluated using a Skin Infection Rating Scale (SIRS). The signs/symptoms parameters evaluated were:

- exudate/pus
- crusting
- erythema/inflammation
- tissue warmth
- edema
- itching
- pain

A score was assigned to each of the above parameters and then a total score was calculated. The scoring scale was as follows:

0=absent=	no evidence of the signs or symptoms
1	
2=mild=	signs/symptoms are present but not intense
3	
4=moderate=	signs/symptoms are clearly evident and are somewhat bothersome to the patient
5	
6=severe=	signs/symptoms are clearly evident, intense, and extremely bothersome to the patient

The 1, 3 and 5 scores are half-scale evaluations with no written definition.

The bacteriology specimens were obtained by swabs of the lesion and cultured according to standard techniques. Swab specimens were acceptable because it was necessary to confirm the presence of white blood cells in the specimen to be cultured.

6. Safety evaluation: The incidence of adverse experiences was compared between the two treatment groups.
7. Pharmacoeconomic assessments: These data will not be analyzed in the review. However, the NDA does state (volume 20, p. 10), "There was no difference found in direct medical resource utilization between treatment groups."

Results: Efficacy evaluations were performed on Intent-to-Treat (ITT) populations at end of therapy and follow-up for the clinical ITT population (all patients randomized to medication) and the bacteriological ITT population (all patients randomized to medication who had a pre-treatment pathogen).

Efficacy evaluations were also performed on "Per Protocol" populations (those patients who did not have a protocol violation during the study). The per protocol evaluability standards (taken directly from volume 20, pp. 40-42 of the NDA):

a. *Clinical Per Protocol Population at End of Therapy*

A patient was clinically evaluable at end of therapy (included in the clinical per protocol population) if the patient:

- met all study entry criteria and had an appropriate secondarily infected wound
- received at least 80% of the study medication as determined by the diary card. Non-compliance was considered a protocol violation. Compliance was defined as having received at least 80% of the prescribed doses of cephalexin (40 x 0.8=32) and at least 80% of the applications of mupirocin (30 x 0.8=24). This was determined from diary card information.
- received treatment for 10 days, 3 days of treatment for clinical failures
- returned for clinical evaluation, preferably all visits, but minimally the end-of-therapy visit

- had not used any prohibited concomitant medications (any topical product, systemic antibiotics, systemic steroids)
- started medications at preliminary visit or within 2 days thereof
- had a clinical EOT assessment of success or failure (not unable to determine)

b. *Clinical Per Protocol Population at Follow-Up*

This was a subset of the clinically evaluable per protocol population at EOT. A patient was clinically evaluable at follow-up (was included in the clinical per protocol population) if the patient:

- had a clinical efficacy assessment at EOT of "clinical success" or "clinical failure"
- follow-up (FU) clinical efficacy assessment was NOT "unable to determine" (unless the patient was a clinical failure at EOT)
- had a FU clinical efficacy assessment within 7-12 days after stopping study medication (except for "clinical recurrence", for whom the window was one day after EOT visit to twelve days after stopping study medication)

c. *Bacteriological Per Protocol Population at EOT*

A patient was bacteriologically evaluable EOT (was included in the bacteriological per protocol population) if:

- the patient was in the Clinical Per Protocol described in a) above
- the patient had a pre-therapy bacterial pathogen isolated from a specimen taken from the wound -2 to 0 days pretreatment
- white blood cells were recovered from the wound (identified on Gram stain or Wright stain)
- the EOT bacteriological assessment was NOT "unable to determine"
- culture date for pathogen on EOT bacteriology page was same as EOT visit date or date of failure

d. *Bacteriological Per Protocol Population at Follow-Up*

This was a subset of the bacteriological per protocol population at EOT. A patient was bacteriologically evaluable at FU (was included in the bacteriological per protocol population) if:

- the patient was bacteriologically evaluable per protocol at EOT
- FU bacteriological assessment was NOT "unable to determine"
- culture date for pathogen on FU bacteriology page was same as FU visit date or date of relapse

**Reviewer's Comment:** The standards for efficacy evaluation as outlined above are acceptable to the reviewers.

**Reviewer's Note:** Some of the tables used in the review of this study are from the NDA. As the table is introduced, the location of the table in the NDA will be cited by volume, page and NDA table number. The following paragraph is taken from p. 6 of Dr. Bell's statistical review. It presents the judgement of the clinical reviewers as well as that of the statistician.

Throughout the phase III development of this drug for this indication, there was ongoing communication between the applicant and the FDA regarding necessary requirements for demonstrating the product's efficacy and safety. There was confirmed agreement on the protocol including inclusion/exclusion criteria, evaluability criteria, and outcome assessment. As a result, the NDA submission for the two pivotal clinical studies included all information needed for the FDA reviewers to confirm that the applicant had conformed to the agreed to protocol. Since the clinical and statistical reviewer were able to verify the integrity of the applicant's database, it was not necessary to produce a separate database based upon the clinical reviewer's patient assessments for analysis.

Demographics: The following table (volume 20, p. 44, Table 3) summarizes the number of patients randomized to drug, those who completed the study, and the number valid for efficacy analyses (by the applicant's evaluation).

Table 1 The number of patients screened and randomized into the study as well as the number who completed the study and who were evaluable in the efficacy analyses.

Number of Patients	Mupirocin Calcium Cream	Cephalexin	Total
Screened			
Randomized	--	--	351
Completed Study	162	171	333
Valid for Efficacy Analyses	141	150	291
Per protocol clinical at FU			
Per protocol clinical at EOT	115	119	234
Per protocol bacteriological at FU	126	131	257
Per protocol bacteriological at EOT	47	57	104
Intent-to-treat clinical at FU*	56	62	118
Intent-to-treat clinical at EOT*	162	171	333
Intent-to-treat bacteriological at FU	162	171	333
Intent-to-treat bacteriological at EOT	95	112	207
	95	112	207

Data Source: Section 11 Table 11.2 and Appendix B, Patient Listings 4-7, 45 and 46

FU=Follow-up; EOT=End of Therapy

\* Clinical intent-to-treat at follow-up and end of therapy=all randomized patients

The following table (volume 20, p. 50, Table 7a) summarizes the demographics for the Intent-to-Treat and Per Protocol at follow-up populations who were clinically evaluable.

Table 2 Demographic characteristics of all randomized\* patients, as well as those in the per protocol clinical analyses at follow-up

Demographic Characteristics	Intent-to-Treat (ITT)				Per-Protocol (PP)			
	Mupirocin Calcium Cream (N = 162)		Cephalexin (N = 171)		Mupirocin Calcium Cream (N = 115)		Cephalexin (N = 119)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Sex</b>								
Male	91	(56.2)	89	(52.0)	63	(54.8)	70	(58.8)
Female	71	(43.8)	82	(48.0)	52	(45.2)	49	(41.2)
<b>Age (years)</b>								
< 2	1	(0.6)	2	(1.2)	0	(0.0)	2	(1.7)
2 - 11	24	(14.8)	33	(19.3)	17	(14.8)	27	(22.7)
12 - 16	15	(9.3)	12	(7.0)	9	(7.8)	11	(9.2)
17 - 45	80	(49.4)	81	(47.4)	56	(48.7)	55	(46.2)
46 - 65	26	(16.0)	25	(14.6)	20	(17.4)	15	(12.6)
> 65	16	(9.9)	18	(10.5)	13	(11.3)	9	(7.6)
Mean $\pm$ SD	33.94 $\pm$ 21.0		32.98 $\pm$ 22.5		35.12 $\pm$ 21.1		29.58 $\pm$ 21.0	
Minimum								
Maximum								
<b>Race</b>								
Caucasian	115	(71.0)	135	(78.9)	81	(70.4)	95	(79.8)
Black	15	(9.3)	11	(6.4)	13	(11.3)	7	(5.9)
Oriental	5	(3.1)	4	(2.3)	5	(4.3)	3	(2.5)
Other	27	(16.7)	21	(12.3)	16	(13.9)	14	(11.8)

Data Source: Appendix B, Patient Listings 9, 10 and 45

\* All randomized patients = intent-to-treat clinical population

**Reviewer's Comment #1:** As previously agreed by the applicant and FDA, the primary effectiveness parameter in this study was clinical response at follow-up. The demographic information presented here is unremarkable, except for the notation that essentially no patients under the age of 2 years were evaluated at follow-up in this study.

**Reviewer's Comment #2:** In the remainder of the data presentations the data generated by Dr. Robert Fiddes (Study Center 011) have not been evaluated at the recommendation of FDA's Division of Scientific Investigations.

The following table is the same as Table 1 above, with the exception that the patients from study center 11 have been deleted from it, as well as from all tables after this.

**Table 3** The number of patients screened and randomized into the study as well as the number who completed the study and who were evaluable in the efficacy analyses excluding center 11.

Number of Patients	Mupirocin Calcium Cream	Cephalexin	Total
Screened	--	--	311
Randomized	144	149	293
Completed Study	125	130	255
Valid for Efficacy Analyses			
Per protocol clinical at FU	103	101	204
Per protocol clinical at EOT	112	113	225
Per protocol bacteriological at FU	41	47	88
Per protocol bacteriological at EOT	48	52	100
Intent-to-treat clinical at FU*	144	149	293
Intent-to-treat clinical at EOT*	144	149	293
Intent-to-treat bacteriological at FU	80	95	175
Intent-to-treat bacteriological at EOT	80	95	175

The following table summarizes the demographics for the Intent-to-Treat and Per Protocol at follow-up populations who were both clinically and bacteriologically evaluable.

**Table 4** Demographic characteristics of patients in the intent-to-treat and per protocol bacteriological analyses at follow-up for Study 129A excluding center 11

Demographic Characteristics	Intent-to-Treat (ITT)				Per Protocol (PP)			
	Mupirocin Calcium Cream (N = 80)		Cephalexin (N = 95)		Mupirocin Calcium Cream (N = 41)		Cephalexin (N = 47)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Sex</b>								
Male	44	(55.0)	53	(55.8)	19	(46.3)	30	(63.8)
Female	36	(45.0)	42	(44.2)	22	(53.7)	17	(36.2)
<b>Age (years)</b>								
< 2	0	(0.0)	2	(2.1)	0	(0.0)	2	(4.3)
2-11	15	(18.8)	15	(15.8)	8	(19.5)	9	(19.1)
12-16	5	(6.3)	5	(5.3)	3	(7.3)	3	(6.4)
17 - 45	42	(52.5)	47	(49.5)	22	(53.7)	22	(46.8)
46-65	13	(16.3)	15	(15.8)	7	(17.1)	7	(14.9)
> 65	5	(6.3)	11	(11.6)	1	(2.4)	4	(8.5)
Mean SD	32.67 <sub>+</sub> 19.4		34.86 <sub>+</sub> 23.0		31.05 <sub>+</sub> 18.2		31.55 <sub>+</sub> 22.3	
Minimum								
Maximum								
<b>Race</b>								
Caucasian	59	(73.8)	79	(83.2)	26	(63.4)	41	(87.2)
Black	9	(11.3)	8	(8.4)	8	(19.5)	5	(10.6)
Oriental	2	(2.5)	2	(2.1)	2	(4.9)	0	(0.0)
Other	10	(12.5)	6	(6.3)	5	(12.2)	1	(2.1)

**Reviewer's Comment:** The per protocol bacteriologically evaluable patient population at follow-up is 88/204 = 43% of the per protocol clinically evaluable patient population (Study Center 011 deleted). This fails to meet the 50% standard for skin and skin structure studies set in the "Points to Consider" for clinical development of anti-infective drugs.

This lower percentage of bacteriologically evaluable patients is partially caused by the decision to exclude from microbiological evaluation all patients enrolled prior to April 17, 1995. Recall that prior to April, 1995, there was no requirement for confirmation of WBCs in the wound exudate in order to be included in the study.

It is felt that this deficiency need not invalidate the study as long as the clinically evaluable patient results and the bacteriologically evaluable patient results are similar.

Wound Description: The following table describes the wounds incurred by the Intent-to-Treat and Per Protocol clinically evaluable populations at entry.

**Table 5 Distribution of type and duration of wound (Intent-to-treat\* and per protocol clinical populations at follow-up) up for Study 129A excluding center 11**

	Intent-to-Treat (ITT)		Per-Protocol (PP)					
	Mupirocin Calcium Cream (N=144)		Cephalexin (N=149)		Mupirocin Calcium Cream (N=103)		Cephalexin (N=101)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Type of Wound</b>								
Small laceration	34	(23.6)	35	(23.5)	30	(29.1)	25	(24.8)
Sutured wound	39	(27.1)	34	(22.8)	25	(24.3)	24	(23.8)
Abrasion	46	(31.9)	54	(36.2)	32	(31.1)	39	(38.6)
Other	25	(17.4)	26	(17.4)	16	(15.5)	13	(12.9)
<b>Site of Wound</b>								
Face, neck	23	(16.0)	22	(14.8)	19	(18.4)	14	(13.9)
Anterior trunk	6	(4.2)	8	(5.4)	5	(4.9)	7	(6.9)
Arms	4	(2.8)	6	(4.0)	0	(0.0)	4	(4.0)
Forearms	12	(8.3)	7	(4.7)	8	(7.8)	3	(3.0)
Palms	9	(6.3)	8	(5.4)	7	(6.8)	5	(5.0)
Thighs	3	(2.1)	4	(2.7)	3	(2.9)	3	(3.0)
Knees	5	(3.5)	13	(8.7)	3	(2.9)	8	(7.9)
Legs	25	(17.4)	26	(17.4)	13	(12.6)	19	(18.8)
Feet (dorsal)	6	(4.2)	9	(6.0)	5	(4.9)	8	(7.9)
Scalp, neck	6	(4.2)	4	(2.7)	5	(4.9)	3	(3.0)
Back	2	(1.4)	5	(3.4)	2	(1.9)	4	(4.0)
Buttocks	1	(0.7)	0	(0.0)	1	(1.0)	0	(0.0)
Elbows	3	(2.1)	3	(2.0)	2	(1.9)	3	(3.0)
Hand (dorsal)	36	(25.0)	32	(21.5)	27	(26.2)	18	(17.8)
Soles	3	(2.1)	2	(1.3)	3	(2.9)	2	(2.0)

\*All randomized patients = intent-to-treat clinical population

The following table describes the wounds incurred by the Intent-to-Treat and Per Protocol bacteriologically evaluable populations at entry.

**Table 6 Distribution of type and duration of wound (Intent-to-treat and per protocol bacteriological populations at follow-up) up for Study 129A excluding center 11**

	Intent-to-Treat (ITT)				Per-Protocol (PP)			
	Mupirocin Calcium Cream (N = 80)		Cephalexin (N = 95)		Mupirocin Calcium Cream (N = 41)		Cephalexin (N = 47)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Type of Wound</b>								
Small laceration	18	(22.5)	25	(26.3)	11	(26.8)	9	(19.1)
Sutured wound	15	(18.8)	18	(18.9)	7	(17.1)	11	(23.4)
Abrasion	31	(38.8)	34	(35.8)	16	(39.0)	21	(44.7)
Other	16	(20.0)	18	(18.9)	7	(17.1)	6	(12.8)
<b>Site of Wound</b>								
Face, neck	13	(16.3)	14	(14.7)	6	(14.6)	9	(19.1)
Anterior trunk	3	(3.8)	6	(6.3)	3	(7.3)	5	(10.6)
Arms	2	(2.5)	4	(4.2)	0	(0.0)	1	(2.1)
Forearms	4	(5.0)	5	(5.3)	2	(4.9)	2	(4.3)
Palms	4	(5.0)	6	(6.3)	1	(2.4)	1	(2.1)
Thighs	3	(3.8)	3	(3.2)	3	(7.3)	1	(2.1)
Knees	3	(3.8)	9	(9.5)	1	(2.4)	5	(10.6)
Legs	18	(22.5)	16	(16.8)	8	(19.5)	10	(21.3)
Feet (dorsal)	4	(5.0)	7	(7.4)	1	(2.4)	3	(6.4)
Scalp, neck	3	(3.8)	1	(1.1)	2	(4.9)	0	(0.0)
Back	2	(2.5)	2	(2.1)	2	(4.9)	1	(2.1)
Buttocks	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Elbows	3	(3.8)	2	(2.1)	2	(4.9)	1	(2.1)
Hand (dorsal)	16	(20.0)	18	(18.9)	9	(22.0)	7	(14.9)
Soles	2	(2.5)	2	(2.1)	1	(2.4)	1	(2.1)

**Reviewer's Comment:** The treatment groups are sufficiently comparable to permit acceptance of the study. The "Other" category in the wound type is mostly characterized by infected human scratches and infections as a result of body piercing. The wounds seen in the study are sufficiently similar that a separate analysis of efficacy by wound type is not needed.

**Patient Withdrawals and Exclusions:** The following table gives the reasons for withdrawal of patients from the study.

**Table 7 The number (%) of randomized patients who completed the study or were withdrawn by the reason for study withdrawal for Study 129A excluding Center 11**

Reason for Study Conclusion	Mupirocin Calcium Cream (N = 144)		Cephalexin (N = 149)	
	n	(%)	n	(%)
Completed study*	125	(86.8)	130	(87.2)
Withdrawal due to:				
Adverse experience	5	(3.5)	5	(3.4)
Lack of efficacy	5	(3.5)	5	(3.4)
Deviation from protocol	1	(0.7)	2	(1.3)
Lost to follow-up	6	(4.2)	4	(2.7)
Other reason	2	(1.4)	3	(2.0)

\* Patients who completed the study as planned met all study entry criteria, completed the 10-day dosing phase of the study, and returned for an EOT and FU visit, irrespective of their clinical outcomes.

**Reviewer's Comment:** The withdrawals due to adverse reactions will be discussed in the safety summary below. The "Other reason" category in Table 7 above included patients who were unable to keep their appointments (1), or missed the end of therapy visit (1) for Bactroban; withdrew for non-medical reasons (1), lost their medication (1), or had their medication stolen (1) for cephalexin.

The following table gives the reasons for exclusion of patients from the clinically evaluable patient base at follow-up.

**Table 8 Reasons for Exclusion from Per Protocol Analysis of Clinical Efficacy at Follow-up Excluding Center 11**

	Mupirocin Calcium Cream (N = 144)		Cephalexin (N = 149)	
	n	(%)	n	(%)
Non-Evaluable (NE)	41	(28.5%)	48	(32.2%)
Reasons for NE				
FU Clin Assess. Is Unable To Determine	23		22	
FU Visit Out of Window	20		24	
Not Clinically Evaluable at EOT	32		36	
Prohibited Med Between EOT & FU	5		3	
-----				
Evaluable	103	(71.5%)	101	(67.8%)

The following table gives the reasons for exclusion of patients from the bacteriologically evaluable patient base at follow-up.

**Table 9 Reasons for Exclusion from Per Protocol Analysis of Bacteriological Efficacy at Follow-up Excluding Center 11**

	Mupirocin Calcium Cream (N = 144)		Cephalexin (N = 149)	
	n		n	
Non-Evaluable (NE)	103 (71.5%)		102 (68.5%)	
Reasons for NE				
FU Visit Out of Window	20		18	
Not Bacteriologically Evaluable at EOT	96		97	
Not Clinically Evaluable FU	41		48	
Evaluable	41 (28.5%)		47 (31.5%)	

Reviewer's Comment: The total of patients in the individual entries for non-evaluability is greater than the actual number of non-evaluables because some patients were assessed as having multiple reasons for non-evaluability.

Effectiveness Parameters: As previously noted, the primary effectiveness parameter in this study was clinical response at follow-up. The results are presented in the following table.

**Table 10 Clinical response at follow-up (per protocol clinical population) for Study 129A excluding Center 11**

Clinical Response	Mupirocin Calcium Cream (N = 103)		Cephalexin (N = 101)		95% Confidence Interval		
	n	(%)	n	(%)	LCL	UCL	p-value
Persistent Clinical Success	97	(94.2)	94	(93.1)	-6.58	8.79	0.747
Recurrence	0	(0.0)	1	(1.0)			
Clinical Failure at EOT	6	(5.8)	6	(5.9)			

The following table presents the clinical response at the end of therapy.

**Table 11 Clinical response at end of therapy Per Protocol Clinical Population at End of Therapy for Study 129A excluding Center 11**

Clinical Response	Mupirocin Calcium Cream		Cephalexin		95% Confidence Limits	
	n/N	(%)	n/N	(%)	LCL	UCL
Clinical Success	106/112	(94.6)	104/113	(92.0)	-4.79	10.00
Failure	6/112	(5.4)	9/113	(8.0)		

**Reviewer's Comment:** It can be seen from Table 10 (Clinical response at follow-up) and Table 11 (Clinical response at end of therapy) that the number of failures in the cephalexin group decreased from 9 at end of therapy to 6 at follow-up. By prior agreement with the applicant, all failures were to be carried forward at follow-up. Therefore, the CRF's for the failures in the cephalexin group were checked. It was found that the evaluators had not carried these failures forward because the follow-up visit was outside the predetermined window of 7-12 days. Therefore, the correct number of failures in the cephalexin group at follow-up is 9/104 = 8.6%. Please see the Efficacy Summary for a revised representation of Table 10. Clinical success rates in the ITT population were 77.8% for mupirocin and 78.9% for cephalexin.

The following table presents the bacteriological response at follow-up.

**Table 12 Bacteriological response at follow-up (per protocol bacteriological population) for Study 129A excluding center 11**

Bacteriological Response	Mupirocin Calcium Cream (N = 41) (N = 47)		Cephalexin Interval		95% Confidence		
	n	(%)n	(%)	LCL	UCL	p-value	
Success	39	(95.1)	46	(97.9)	-12.81	7.31	0.478
Failure	2	(4.9)	1	(2.1)			

The following table presents the bacteriological response at the end of therapy.

**Table 13 Bacteriological response at end of therapy Per Protocol Bacteriological Population at End of Therapy for Study 129A excluding Center 11**

Bacteriological Response	Mupirocin Calcium Cream		Cephalexin	
	n/N	(%)	n/N	(%)
Success	46/48	(95.8)	51/52	(98.0)
Failure	2/48	(4.2)	1/52	(2.0)

**Reviewer's Comment:** These products were both extremely effective in bacteriological response, and this response is quite similar to the clinical response. The clinical response rates for the fully evaluable patient populations at follow-up are the same as noted in Table 12 (95.1% for mupirocin calcium and 97.9% for cephalexin). Bacteriological success rates in the ITT populations at follow-up were 75.8% for mupirocin and 78.6% for cephalexin.

The following table presents a summary of the disease sign and symptom (SIRS) scores.

**Table 14**  
**Summary of Skin Infection Rating Scale Data**  
**Per Protocol Clinical Population at Follow-up**  
**Excluding Center 11**

		Mupirocin Calcium Cream							Cephalexin							p-value		
		0	1	2	3	4	5	6	N	0	1	2	3	4	5		6	N
Exudate/ pus	Preliminary	3	9	33	22	23	10	3	103	4	8	34	23	24	6	2	101	0.493
	On Therapy	51	23	20		5	3	1	103	44	24	23	7	2		1	101	0.514
	End of Therapy	97	1	3		1			102	97		1	1	1			100	0.810
	Follow-up	96	3						99	95			1	1			97	0.435
Crusting	Preliminary	13	10	26	21	29	3	1	103	19	5	20	12	34	11		101	0.493
	On Therapy	27	31	30	12	3			103	31	21	26	19	2	2		101	0.482
	End of Therapy	69	20	10	2	1			102	58	23	16	1	2			100	0.170
	Follow-up	78	14	5	2				99	77	15	3	1	1			97	0.880
Erythema/ Inflam	Preliminary		1	24	22	40	14	2	103	1	5	22	22	35	13	3	101	0.462
	On Therapy	10	33	44	8	7		1	103	9	35	42	9	5	1		101	0.757
	End of Therapy	42	49	10	1				102	43	37	15	2	3			100	0.218
	Follow-up	75	24						99	64	28	2	2	1			97	0.028
Tissue Warmth	Preliminary	14	25	19	20	22	3		103	18	18	30	17	16	2		101	0.350
	On Therapy	52	39	10	1	1			103	63	21	10	6	1			101	0.889
	End of Therapy	96	5	1					102	92	6	2					100	0.496
	Follow-up	98	1						99	92	3	1	1				97	0.082
Tissue Edema	Preliminary	15	23	22	23	16	3	1	103	14	17	34	14	18	3	1	101	0.870
	On Therapy	51	23	25	2	1	1		103	47	24	24	5	1			101	0.741
	End of Therapy	85	15	2					102	78	15	6		1			100	0.124
	Follow-up	91	7	1					99	88	7		1	1			97	0.411
Itching	Preliminary	66	17	9	4	4	2	1	103	54	9	19	5	11	1	2	101	0.029
	On Therapy	82	12	8			1		103	67	17	14	2	1			101	0.052
	End of Therapy	93	6	2	1				102	83	11	3	2	1			100	0.091
	Follow-up	97	2						99	87	7	1	1	1			97	0.019
Pain	Preliminary	11	14	23	21	26	4	4	103	10	12	32	16	23	3	5	101	0.827
	On Therapy	62	17	12	6	4	1	1	103	63	20	14	3			1	101	0.194
	End of Therapy	94	7	1					102	89	7	3	1				100	0.228
	Follow-up	96	2	1					99	92	3	1					97	0.334

**Reviewer's Comment:** There were no statistically significant differences in SIRS scores at either end of treatment or follow-up except for itching and erythema at follow-up. Both these differences were in favor of mupirocin although itching was worse in the cephalexin group at baseline.

Microbiological Results: The following table presents the eradication rate for each pathogen seen in the pre-therapy culture for the patient population which was bacteriologically evaluable at follow-up.

**Table 15**  
**Bacteriological Eradication Rate for Each Pathogen at Follow-up**  
**Per Protocol Bacteriological Population at Follow-up**

Organism Classification	Mupirocin Calcium Cream			Cephalexin		
	Prelim	Follow-up	Erad Rate (%)	Prelim	Follow-up	Erad Rate (%)
<b>Gram-positive aerobes</b>						
<i>Bacillus cereus</i>	1	0	100	0	0	
<i>Bacillus species</i>	2	0	100	5	0	100
<i>Enterococcus</i>	2	0	100	3	0	
<i>Staphylococcus aureus</i>	21	0	100	26	0	100
<i>Streptococcus</i> Group A	2	0	100	7	0	100
<i>Streptococcus</i> Group B	0	0		2	0	100
<i>Streptococcus</i> Group G	0	0		1	0	100
<i>Streptococcus beta hemolytic</i>	1	0	100	0	0	
<b>Gram-negative aerobes</b>						
<i>Acinetobacter baumannii</i>	2	0	100	4	0	100
<i>Acinetobacter lwoffii</i>	3	0	100	1	0	100
<i>Acinetobacter junii johnsonii</i>	0	0		1	0	100
<i>Aeromonas hydrophilia</i>	1	0	100	0	0	
<i>Agrobacterium radiobacter</i>	0	0		0	0	100
<i>Chryseomonas luteola</i>	0	0		1	0	100
<i>Comamonas testosteroni</i>	0	0		1	0	100
<i>Comamonas acidovorans</i>	0	0		1	0	100
<i>Enterobacter agglomerans</i>	3	0	100	0	0	
<i>Enterobacter cloacae</i>	3	0	100	0	0	
<i>Escherichia coli</i>	0	0		1	0	100
<i>Flavimonas oryzihabitans</i>	1	0	100	4	0	100
<i>Flavobacterium species</i>	0	0		1	0	100
<i>Klebsiella oxytoca</i>	3	0	100	1	0	100
<i>Klebsiella pneumoniae</i>	1	0	100	1	0	100
<i>Morganella morgani</i>	1	0	100	0	0	
<i>Moraxella species</i>	1	0	100	3	0	100
<i>Ochrobactrum anthropi</i>	0	0		1	0	100
<i>Proteus mirabilis</i>	1	0	100	0	0	
<i>Pseudomonas aeruginosa</i>	1	0	100	3	0	100
<i>Pseudomonas fluorescens</i>	0	0		1	0	100
<i>Pseudomonas putida</i>	1	0	100	2	0	100
<i>Pseudomonas vesicularis</i>	0	0		1	0	100
<i>Serratia liquifaciens</i>	1	0	100	1	0	100
<i>Serratia marcescens</i>	1	0	100	1	0	100
<i>Sphingobacterium multivorum</i>	1	0	100	0	0	
<i>Sphingobacterium spritivorum</i>	0	0		1	0	100
<b>Gram-positive anaerobes</b>						
<i>Propionibacterium species</i>	0	0		1	0	100
<b>Gram-negative anaerobes</b>						
<i>Actinobacillus species</i>	1	0	100	0	0	
<i>Kluyvera species</i>	0	0		1	0	100

**Reviewer's Comment:** The applicant notes (volume 20, p. 65 of the NDA) that of the thirteen pathogens listed in the Intent-to-treat patient population as not eradicated by Bactroban, all were assumed to be not eradicated because data were lacking; not because persistence was established by analysis. All pathogens in the per protocol patient populations were eradicated. The reviewers are not convinced that all the pre-therapy isolates are the causative pathogens in the mild infections seen in this study. Since most were isolated infrequently, they will not be considered for inclusion in the labeling.

**Safety:** The applicant reports that 31/162 (19.1%) of patients randomized to Bactroban reported a total of 50 adverse experiences. Similarly, 40/171 (23.4%) of patients randomized to cephalexin reported a total of 62 adverse events. (The results include study Center 11). The majority of these events were not related to drug therapy. The following table presents the adverse events for each drug which were judged to be possibly or probably related to drug therapy.

Table 16 Adverse experiences (AEs) considered by the investigator to be related or possibly related to treatment in descending order of frequency by mupirocin calcium cream for Study 129A excluding Center 11

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N = 144)		Cephalexin (N = 149)	
	n	(%)	n	(%)
Nausea	2	(1.4)	2	(1.3)
Dermatitis	1	(0.7)	0	(0.0)
Dizziness	1	(0.7)	0	(0.0)
Infection	1	(0.7)	0	(0.0)
Stomatitis ulcerative	1	(0.7)	0	(0.0)
Therapeutic response increased	1	(0.7)	0	(0.0)
Application site reaction	1	(0.7)	1	(0.7)
Headache	1	(0.7)	1	(0.7)
Diarrhea	1	(0.7)	5	(3.4)
Abdominal pain	0	(0.0)	1	(0.7)
Anorexia	0	(0.0)	1	(0.7)
Constipation	0	(0.0)	1	(0.7)
Feces discolored	0	(0.0)	1	(0.7)
Moniliasis genital	0	(0.0)	1	(0.7)
Pruritus	0	(0.0)	1	(0.7)
Pruritus genital	0	(0.0)	1	(0.7)
Urticaria	0	(0.0)	1	(0.7)
Total patients w/adverse experiences*	10	(6.9)	13	(8.7)

\*Note: Some patients had more than one reaction

**Reviewer's Comment:** The case report tabulations (and case report forms, where indicated) have been reviewed to assess whether the judgements of the investigators concerning the relationship of the drugs to the adverse reactions seen are justified. Of the 50 reactions seen in the Bactroban group, the reviewers have found those listed in the following table to be probably or possibly associated with Bactroban therapy. It should be noted that systemic subjective reactions (nausea, dizziness, headache) have not been changed by the reviewers.

Table 17 (n = 144)

Adverse Events	n	(%)
Nausea	2	1.4
Rash	2	1.4
Dermatitis	1	0.7
Dizziness	1	0.7
Application site rx.	1	0.7
Headache	1	0.7
Ulcerative stomatitis	1	0.7
Pruritus	1	0.7
Secondary wound inf.	1	0.7
Cellulitis	1	0.7
	<u>12</u>	<u>8.3</u>

The adverse events seen in this study were not serious or unusual. The safety of the use of Bactroban Cream in the small infected lesions studied was satisfactory. Six patients in the Bactroban group withdrew from the study because of a total of 8 adverse reactions. These were: nausea (2), asthenia (1), leg edema (1), infection (not at study site) (1), dermatitis (1), maculopapular rash (1), and peripheral gangrene (1).

**Conclusions:** Study 129A is acceptable as one of the two pivotal studies necessary to demonstrate the safety and effectiveness of Bactroban Cream in the treatment of secondarily infected traumatic skin lesions. Bactroban was clinically and bacteriologically equivalent to cephalexin. Their safety profiles were similar. About half of the infections were due to *S. aureus*, with the remainder spread among various pathogens.

B. **Study Title:** A Comparative Study of the Safety and Efficacy of Mupirocin Calcium Cream with Cephalexin in the Treatment of Secondarily Infected Open Wounds (Study No. BRL 4910F/129B).

**Investigators:** This was a multi-center study conducted at 27 independent centers under a common protocol. The following presentation lists the clinical investigators and the numbers of patients who were in the intent-to-treat (ITT) enrollment for each treatment arm. The presentation also includes the numbers of patients who were clinically (CLIN) evaluable per protocol at follow-up and bacteriologically (BACT) evaluable per protocol at the follow-up visit (Mup=Bactroban; Ceph=Cephalexin). The CV's for the investigators have been reviewed and found acceptable.

<u>Study Center Number/ Investigator/Location</u>	<u>ITT</u>		<u>CLIN</u>		<u>BACT</u>	
	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>
001 Thomas Bock, D.O. David Ginsberg, D.O. Robert Hippert, D.O. Harleysville Medical Assoc. Harleysville, PA	1	1	0	1	0	0
002 Michael Gold, M.D. Clinical Research Assoc. Nashville, TN	9	7	0	1	0	0
003 Margaret Drebohl, M.D. Center for Health Care San Diego, CA	13	13	9	9	4	3
004 Leslie Capin, M.D. Pasquale Dilorenzo, M.D. 4300 Harlan Street Wheat Ridge, CO	49	49	39	38	7	5
006 James Jupa, M.D. Deerpath Medical Assoc. Lake Bluff, IL	1	0	0	0	0	0
009 Michael Chin, M.D. University of Texas Dallas, TX	1	1	0	0	0	0
017 Robert Howard, M.D. 1301 Memorial Drive Bryan, TX	11	9	8	3	5	2
018 Jon Salisbury, M.D. Eatontown Medical Assoc. Eatontown, NJ	1	1	1	1	1	1
021 John Ondrejicka, M.D. Health Trials 3000 Jacksonville Beach, FL	1	0	1	0	1	0
022 Mark Weinstein, M.D. Volunteers in Pharm. San Antonio, TX	0	1	0	1	0	1
025 Scott Clark, M.D. Longmont Clinic Longmont, CO	7	6	7	3	3	0

<u>Study Center Number/ Investigator/Location</u>	<u>ITT</u>		<u>CLIN</u>		<u>BACT</u>	
	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>
027 Malcom Sperling, M.D. Edinger Medical Group Fountain Valley, CA	11	9	8	6	4	2
029 James Nahlik, M.D. Cheryl Miller, Pharm. D. 4421 N.E. St. Johns Blvd. Vancouver, WA	8	5	1	2	0	2
030 Rohit Desai, M.D. 4421 N.E. St. Johns Blvd. Vancouver, WA	2	2	1	2	1	0
034 Stephen Storfer, M.D. St. Louis Center for Clin. Res. St. Louis, MO	13	13	9	7	3	3
035 Wade Huey, M.D. Harry Rosenthal, M.D. Research for Health Houston, TX	2	2	0	1	0	1
040 William Anderson, M.D. New Mexico Medical Group Rio Rancho, NM	2	0	1	0	0	0
041 Judith Kirstein, M.D. Advanced Clinical Research Salt Lake City, UT	11	10	11	5	5	2
044 Todd Mahr, M.D. Gunderson Clinic La Crosse, WI	6	5	4	3	0	0
055 Christopher Chappel, M.D. Family Practice Assoc. Kissimmee, FL	8	10	5	7	1	3
058 Michael McAdoo, M.D. 6041 Telecom Drive Milan, TN	7	6	5	3	2	0
061 Gerald Bottenfield, M.D. R/D Clinical Research Lake Jackson, TN	9	10	8	9	6	3

<u>Study Center Number/ Investigator/Location</u>	<u>ITT</u>		<u>CLIN</u>		<u>BACT</u>	
	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>
063 Ann Martin, M.D. Washington University St. Louis, MO	3	3	1	0	0	0
065 Willis Gooch, III, M.D. Medical Research Assoc. Salt Lake City, UT	8	7	5	5	4	4
066 Anne Lucky, M.D. Dermatology Research Assoc. Cincinnati, OH	1	1	0	1	0	1
070 Raymond Rosenberg, M.D. 1805 Parke Plaza Circle Stone Mountain, GA	9	6	6	5	4	2
076 Carl Sufit, M.D. Gould Medical Found. Modesto, CA	1	1	0	1	0	0
TOTAL	195	178	130	114	51	35

Study Dates: August 31, 1994 - June 17, 1996.

Study Objectives: These were the same as described above for Study 129A.

Method: This was the same as described above for Study 129A. A total of 373 patients were randomized to receive study medication (195 Bactroban, 178 cephalixin).

Results: Efficacy evaluations were performed on the same populations as described above for Study 129A.

Reviewer's Comment: The clinical reviewer and the statistician have compared the data base in the submitted paper NDA and in the electronic NDA for accuracy and quality assurance that the data items were the same. When this was done, no inconsistencies were found. The data base has also been examined for accuracy and consistency of clinical judgements concerning patient evaluability and found to be satisfactory. Therefore, the results presented by the applicant are accepted. However, please see the comment under Effectiveness Parameters below.

Demographics: The following table (volume 25, p. 45, Table 3) summarizes the number of patients randomized to drug, those who completed the study, and the number valid for efficacy analyses.

**Table 1** The number of patients screened and randomized into the study as well as the number who completed the study and who were evaluable in the efficacy analyses.

Number of Patients	Mupirocin Calcium Cream	Cephalexin	Total
Screened	---	--	418
Randomized	195	178	373
Completed Study	176	163	339
Valid for Efficacy Analyses			
Per protocol clinical at FU	130	114	244
Per protocol clinical at EOT	144	127	271
Per protocol bacteriological at FU	51	35	86
Per protocol bacteriological at EOT	59	40	99
Intent-to-treat clinical at FU*	195	178	373
Intent-to-treat clinical at EOT*	195	178	373
Intent-to-treat bacteriological at FU	115	82	197
Intent-to-treat bacteriological at EOT	115	82	197

Data Source: Section 11 Table 11.2 and Appendix B, Patient Listings 4-7, and 45

FU= Follow-up; EOT= End of Therapy

\* Clinical intent-to-treat at follow-up and end of therapy = all randomized patients

The following table (volume 25, p. 52, Table 7a) summarizes the demographics for the Intent-to-Treat and Per Protocol at follow-up populations who were clinically evaluable.

**Table 2** Demographic characteristics of all randomized\* patients, as well as those in the per protocol clinical analyses at follow-up

Demographic Characteristics	Intent-to-Treat (ITT)				Per-Protocol (PP)			
	Mupirocin Calcium Cream (N = 195)		Cephalexin (N = 178)		Mupirocin Calcium Cream (N = 130)		Cephalexin (N = 114)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Sex</b>								
Male	96	(49.2)	93	(52.2)	69	(45.4)	56	(49.1)
Female	99	(50.8)	85	(47.8)	71	(54.6)	58	(50.9)
<b>Age (years)</b>								
< 2	3	(1.5)	6	(3.4)	3	(2.3)	5	(4.4)
2 - 11	21	(10.8)	17	(9.6)	13	(10.0)	10	(8.8)
12 - 16	11	(5.6)	15	(8.4)	7	(5.4)	9	(7.9)
17 - 45	92	(47.2)	81	(45.5)	62	(47.4)	53	(46.5)
46 - 65	43	(22.1)	31	(17.4)	28	(21.5)	20	(17.5)
> 65	25	(12.8)	28	(15.7)	17	(13.1)	17	(14.9)
Mean ± SD	38.46 ± 21.1		38.60 ± 22.8		38.08 ± 21.2		38.40 ± 22.6	
Minimum								
Maximum								
<b>Race</b>								
Caucasian	174	(89.2)	162	(91.0)	118	(90.8)	107	(93.9)
Black	12	(6.2)	9	(5.1)	4	(3.1)	2	(1.8)
Oriental	0	----	1	(0.6)	0	----	1	(0.9)
Other	9	(4.6)	6	(3.4)	8	(6.2)	4	(3.5)

Data Source: Appendix B, Patient Listings 9, 10 and 45

\* All randomized patients = intent-to-treat clinical population

The following table (volume 25, p. 53, Table 7b) summarizes the demographics for the Intent-to-Treat and Per Protocol at follow-up populations who were both clinically and bacteriologically evaluable.

**Table 3 Demographic characteristics of patients in the intent-to-treat and per protocol bacteriological analyses at follow-up**

Demographic Characteristics	Intent-to-Treat (ITT)		Per-Protocol (PP)	
	Mupirocin Calcium Cream (N = 115)	Cephalexin (N = 82)	Mupirocin Calcium Cream (N = 51)	Cephalexin (N = 35)
	n (%)	n (%)	n (%)	n (%)
<b>Sex</b>				
Male	58 (50.4)	44 (53.7)	24 (47.1)	21 (60.0)
Female	57 (49.6)	38 (46.3)	27 (52.9)	14 (40.0)
<b>Age (years)</b>				
< 2	3 (2.6)	3 (3.7)	3 (5.9)	3 (8.6)
2 - 11	15 (13.0)	9 (11.0)	9 (17.6)	6 (17.1)
12 - 16	7 (6.1)	9 (11.0)	3 (5.9)	2 (5.7)
17 - 45	53 (46.1)	37 (45.1)	24 (47.1)	17 (48.6)
46 - 65	21 (18.3)	14 (17.1)	7 (13.7)	5 (14.3)
> 65	16 (13.9)	10 (12.2)	5 (9.8)	2 (5.7)
Mean ± SD	37.06 ± 22.2	35.47 ± 21.7	30.79 ± 20.8	29.21 ± 19.7
Minimum				
Maximum				
<b>Race</b>				
Caucasian	97 (84.3)	72 (87.8)	42 (82.4)	31 (88.6)
Black	10 (8.7)	8 (9.8)	3 (5.9)	2 (5.7)
Oriental	0 ----	1 (1.2)	0 ----	1 (2.9)
Other	8 (7.0)	1 (1.2)	6 (11.8)	1 (2.9)

Data Source: Appendix B, Patient Listings 11, 12 and 45

**Reviewer's Comment:** The per protocol bacteriologically evaluable patient population at follow-up is 86/244=35% of the per protocol clinically evaluable patient population. This fails to meet the 50% standard for skin and skin structure studies set in the "Points to Consider" for clinical development of anti-infective drugs. This low percentage of bacteriologically evaluable patients is partially caused by the decision to exclude from microbiological evaluation all patients enrolled prior to April 17, 1995. Recall that prior to April 1995, there was no requirement for confirmation of WBCs in the wound exudate in order to be included in the study.

It is felt that this deficiency need not invalidate the study as long as the clinically evaluable patient results and the bacteriologically evaluable patient results mirror each other. The demographics as displayed above are otherwise unremarkable, except for the lack of minorities in the patient database.

**Wound Description:** The following table (volume 25, p. 54, Table 8a) describes the wounds incurred by the Intent-to-Treat and Per Protocol clinically evaluable populations at entry.

**Table 4 Distribution of type and duration of wound (Intent-to-treat\* and per protocol clinical populations at Entry)**

	Intent-to-Treat (ITT)		Per-Protocol (PP)					
	Mupirocin Calcium Cream (N = 195)		Cephalexin (N = 178)		Mupirocin Calcium Cream (N = 130)		Cephalexin (N = 114)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Type of Wound</b>								
Small laceration	57	(29.2)	59	(33.1)	41	(31.5)	40	(35.1)
Sutured wound	27	(13.8)	26	(14.6)	20	(15.4)	20	(17.5)
Abrasion	64	(32.8)	50	(28.1)	46	(35.4)	33	(28.9)
Other	47	(24.1)	43	(24.2)	23	(17.7)	21	(18.4)
<b>Duration of Wound</b>								
Mean (days)	8.28		7.36		7.65		7.10	
< 1 day	3	(1.5)	1	(0.6)	0	----	0	----
1 to 5 days	103	(52.8)	103	(57.9)	72	(55.4)	63	(55.3)
> 5 days	89	(45.6)	74	(41.6)	58	(44.6)	51	(44.7)
<b>Site of Wound</b>								
Face, neck	23	(11.8)	30	(16.9)	17	(13.1)	21	(18.4)
Anterior trunk	8	(4.1)	12	(6.7)	7	(5.4)	8	(7.0)
Genitalia	0	-----	2	(1.1)	0	----	0	----
Arms	14	(7.2)	7	(3.9)	7	(5.4)	2	(1.8)
Forearms	13	(6.7)	5	(2.8)	6	(4.6)	5	(4.4)
Palms	16	(8.2)	7	(3.9)	14	(10.8)	5	(4.4)
Thighs	9	(4.6)	2	(1.1)	1	(0.8)	1	(0.9)
Knees	14	(7.2)	13	(7.3)	10	(7.7)	8	(7.0)
Legs	21	(10.8)	22	(12.4)	16	(12.3)	10	(8.8)
Feet (dorsal)	19	(9.7)	8	(4.5)	10	(7.7)	4	(3.5)
Scalp, neck	5	(2.6)	3	(1.7)	3	(2.3)	3	(2.6)
Back	9	(4.6)	10	(5.6)	7	(5.4)	8	(7.0)
Buttocks	1	(0.5)	3	(1.7)	0	----	1	(0.9)
Elbows	2	(1.0)	7	(3.9)	2	(1.5)	5	(4.4)
Hand (dorsal)	37	(19.0)	42	(23.6)	29	(22.3)	31	(27.2)
Soles	4	(2.1)	5	(2.8)	1	(0.8)	2	(1.8)

Data source: Appendix B, Patient Listings 17 and 45

\* All randomized patients = intent-to-treat clinical population

The following table (volume 25, p. 55, Table 8b) describes the wounds incurred by the Intent-to-Treat and Per Protocol bacteriologically populations at entry.

**Table 5 Distribution of type and duration of wound (Intent-to-treat and per protocol bacteriological populations at Entry)**

	Intent-to-Treat (ITT)		Per-Protocol (PP)					
	Mupirocin Calcium Cream (N = 115)		Cephalexin (N = 82)		Mupirocin Calcium Cream (N = 51)		Cephalexin (N = 35)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Type of Wound</b>								
Small laceration	37	(32.2)	29	(35.4)	15	(29.4)	12	(34.3)
Sutured wound	12	(10.4)	8	(9.8)	4	(7.8)	4	(11.4)
Abrasion	35	(30.4)	24	(29.3)	21	(41.2)	10	(28.6)
Other	31	(27.0)	21	(25.6)	11	(21.6)	9	(25.7)
<b>Duration of Wound</b>								
Mean (days)	9.67		7.89		7.57		6.71	
< 1 day	1	(0.9)	1	(1.2)	0	----	0	----
1 to 5 days	54	(47.0)	46	(56.1)	27	(52.9)	21	(60.0)
> 5 days	60	(52.2)	35	(42.7)	24	(47.1)	14	(40.0)
<b>Site of Wound</b>								
Face, neck	11	(9.6)	11	(13.4)	6	(11.8)	5	(14.3)
Anterior trunk	5	(4.3)	7	(8.5)	5	(9.8)	5	(14.3)
Arms	10	(8.7)	2	(2.4)	4	(7.8)	0	----
Forearms	7	(6.1)	3	(3.7)	2	(3.9)	2	(5.7)
Palms	10	(8.7)	2	(2.4)	5	(9.8)	1	(2.9)
Thighs	8	(7.0)	1	(1.2)	1	(2.0)	0	----
Knees	8	(7.0)	5	(6.1)	6	(11.8)	3	(8.6)
Legs	13	(11.3)	11	(13.4)	5	(9.8)	3	(8.6)
Feet (dorsal)	11	(9.6)	4	(4.9)	4	(7.8)	2	(5.7)
Scalp, neck	1	(0.9)	2	(2.4)	0	----	0	----
Back	3	(2.6)	4	(4.9)	1	(2.0)	2	(5.7)
Buttocks	1	(0.9)	3	(3.7)	0	----	0	----
Elbows	2	----	3	(3.7)	0	----	1	(2.9)
Hand (dorsal)	37	(21.7)	22	(26.8)	11	(21.6)	10	(28.6)
Soles	4	(1.7)	2	(2.4)	1	(2.0)	1	(2.9)

Data source: Appendix B, Patient Listings 18 and 45

**Reviewer's Comment:** The treatment groups are sufficiently comparable to permit acceptance of the study. The "Other" category in the wound type is mostly characterized by infected human scratches and infections as a result of body piercing. The wounds seen in the study are sufficiently similar that a separate analyses of efficacy by wound type is not necessary.

Patient Withdrawals and Exclusions: The following table (volume 25, p. 46, Table 5) gives the reasons for withdrawal of patients from the study.

**Table 6 The number (%) of randomized patients who completed the study or were withdrawn by the reason for study withdrawal**

Reason for Study Conclusion	Mupirocin Calcium Cream (N = 195)		Cephalexin (N = 178)	
	n	(%)	n	(%)
Completed study*	176	(90.3)	163	(91.6)
Withdrawal due to:				
Adverse experience	4	(2.1)	0	-----
Lack of efficacy	1	(0.5)	2	(1.1)
Deviation from protocol	6	(3.1)	8	(4.5)
Lost to follow-up	3	(1.5)	5	(2.8)
Other reason	5	(2.6)	0	-----

\*Patients who completed the study as planned met all study entry criteria, completed the 10-day dosing phase of the study, and returned for an EOT and FU visit, irrespective of their clinical outcomes.

Data source: Appendix B, Patient Listings 1 and 2

Reviewer's Comment: The withdrawals due to adverse reactions will be discussed in the safety summary below. The "Other reason" category in Table 6 above included patients who missed the end of therapy visit (2), did not meet eligibility requirements, had a family crisis, and voluntarily withdrew for non-medical reasons.

The following table (volume 25, p. 146, Table 11.7) gives the reasons for exclusion of patients from the clinically evaluable patient base at follow-up.

**Table 7 Reasons for Exclusion from Per Protocol Analysis of Clinical Efficacy at Follow-up (BRL4910F/129B)**

	Mupirocin Calcium Cream (N = 195)	Cephalexin (N = 178)
	N	N
Non-Evaluable (NE)	65 (33.3%)	64 (36%)
Reasons for NE		
FU Clin Assess. Is Unable To Determine	31	26
FU Visit Out of Window	23	22
Not Clinically Evaluable at EOT	51	51
Prohibited Med Between EOT & FU	6	4
-----		
Evaluable	130 (66.7%)	114 (64%)

The following table (volume 25, p. 148, Table 11.9) gives the reasons for exclusion of patients from the bacteriologically evaluable patient base at follow-up.

**Table 8 Reasons for Exclusion from Per Protocol Analysis of Bacteriological Efficacy at Follow-up (BRL4910F/129E)**

	Mupirocin Calcium Cream (N = 195)	Cephalexin (N = 178)
	N	N
Non-Evaluable (NE)	144 (73.8%)	143 (80.3%)
Reasons for NE		
FU Bact Assess. Is Unable To Determine	21	9
Not Bacteriologically Evaluable at EOT	136	138
Not Clinically Evaluable at FU	65	64
-----		
Evaluable	51 (26.2%)	35 (19.7%)

**Reviewer's Comment:** The total of patients in the individual entries for non-evaluability is greater than the actual number of non-evaluables because some patients were assessed as having multiple reasons for non-evaluability.

**Effectiveness Parameters:** As previously noted, the primary effectiveness parameter in this study was clinical response at follow-up. The following table (volume 25, p. 65, Table 13) presents the results of this parameter.

**Table 9 Clinical response at follow-up (per protocol clinical population)**

Clinical Response	Mupirocin Calcium Cream (N = 130)		Cephalexin (N = 114)		95% Confidence Interval		
	n	(%)	n	(%)	LCL	UCL	p-value
Persistent Clinical Success	125	(96.2)	110	(96.5)	-5.00	4.40	0.889
Recurrence	1	(0.8)	2	(1.8)			
Clinical Failure at EOT	4	(3.1)	2	(1.8)			

Data Source: Appendix C, Patient Listing 28

The following table (volume 25, p. 159, Table 12.6) presents the clinical response at the end of therapy.

**Table 10 Clinical response at end of therapy  
Per Protocol Clinical Population at End of Therapy**

Clinical Response	Mupirocin Calcium Cream		Cephalexin		95% Confidence Limits	
	n/N	(%)	n/N	(%)	LCL	UCL
Clinical Success	139/144	(96.5)	125/127	(98.4)	-5.60	1.80
Failure	5/144	(3.5)	2/127	(1.6)		

**Reviewer's Comment:** It can be seen from Table 9 (Clinical response at follow-up) and Table 10 (Clinical response at end of therapy) that the number of failures in the Mupirocin group decreased from 5 at end of therapy to 4 at follow-up. By prior agreement with the applicant, all failures were to be carried forward at follow-up. Therefore, the CRF's for all patients in both groups who were designated as failures at the end of therapy were checked. Two of the Mupirocin failures were in patients who were protocol violations (diagnoses of abscess and cutaneous ulcer, both of which were to be patient exclusions). In addition, one Cephalexin failure which should have been carried forward was not. Therefore, the correct number of failures in the Mupirocin group at follow-up was 3/128 = 2.3% and in the Cephalexin group it was 3/115 = 2.6%. Please see the Efficacy Summary for a revised presentation of Table 9. Clinical success rates in the ITT population were 80.0% for mupirocin and 82.6% for cephalexin.

The following table (volume 25, p. 66, Table 14) presents the bacteriological response at follow-up.

**Table 11 Bacteriological response at follow-up (per protocol bacteriological population)**

Bacteriological Response	Mupirocin Calcium Cream (N = 51)		Cephalexin (N = 35)	
	n	(%)	n	(%)
Success	51	(100.0)	35	(100.0)

Data Source: Appendix C, Patient Listing 32

The following table (volume 25, p. 161, Table 12.9) presents the bacteriological response at the end of therapy.

**Table 12 Bacteriological response at end of therapy Per Protocol Bacteriological Population at End of Therapy**

Bacteriological Response	Mupirocin Calcium Cream		Cephalexin	
	n/N	(%)	n/N	(%)
Success	59/59	(100.0)	40/40	(100.0)

**Reviewer's Comment:** All patients who were bacteriologically evaluable at end of therapy and follow-up were successes. The clinical response rates for the fully evaluable patient populations at follow-up are the same as noted in Table 11 (100% for both medications). Bacteriological success rates in the ITT populations at follow-up were similar (80.0% for mupirocin and 82.9% for cephalexin).

The following table (volume 25, p. 150, Table 12.1) presents a summary of the disease sign and symptom (SIRS) scores.

**Table 13  
Summary of Skin Infection Rating Scale Data  
Per Protocol Clinical Population at Follow-up**

		Mupirocin Calcium Cream								Cephalexin								N	p-value
		0	1	2	3	4	5	6	N	0	1	2	3	4	5	6			
Exudate/ pus	Preliminary	2	14	68	21	23	1	1	130	1	12	52	22	22	1	4	114	0.173	
	On Therapy	92	24	11	3				130	82	19	11	1			1	114	0.881	
	End of Therapy	126	2	1					129	111							111	0.128	
	Follow-up	126	1	1					128	110		1					111	0.829	
Crusting	Preliminary	10	23	46	15	30	5	1	130	20	9	38	20	22	3	2	114	0.539	
	On Therapy	51	38	30	9	2			130	48	30	27	8	1			114	0.755	
	End of Therapy	86	28	13	2				129	84	16	8	2	1			111	0.376	
	Follow-up	106	19	2	1				128	92	13	4	1	1			111	0.508	
Erythema/ Inflam	Preliminary	1	6	31	41	46	3	2	130	1	4	25	32	49	2	1	114	0.524	
	On Therapy	14	54	38	22	2			130	5	46	44	16	2	1		114	0.232	
	End of Therapy	55	53	16	4	1			129	54	42	14	1				111	0.222	
	Follow-up	85	32	8	2	1			128	73	25	9	4				111	0.672	
Tissue Warmth	Preliminary	15	30	50	15	19	1		130	9	22	48	16	17	1	1	114	0.247	
	On Therapy	86	36	6	2				130	71	23	12	7	1			114	0.040	
	End of Therapy	121	6	1	1				129	105	4	2					111	0.772	
	Follow-up	125	2		1				128	107	3	1					111	0.865	
Tissue Edema	Preliminary	7	41	50	18	11	2	1	130	5	26	41	17	24	1		114	0.033	
	On Therapy	64	47	16	3				130	53	29	23	8		1		114	0.046	
	End of Therapy	114	11	2	2				129	92	13	5	1				111	0.307	
	Follow-up	121	5	1		1			128	101	6	4					111	0.473	
Itching	Preliminary	74	18	15	12	7	2	2	130	67	11	17	3	11	1	4	114	0.678	
	On Therapy	91	16	14	2	3	3	1	130	81	13	8	5	7			114	0.964	
	End of Therapy	107	15	4	1	1	1		129	87	13	7	2	2			111	0.336	
	Follow-up	123	3	1		1			128	100	6	4			1		111	0.142	
Pain	Preliminary	26	16	46	11	24	5	2	130	20	21	33	14	18	6	2	114	0.904	
	On Therapy	79	25	23	2	1			130	72	23	11	3	3	2		114	0.734	
	End of Therapy	122	4	1		2			129	101	6	3	1				111	0.690	
	Follow-up	122	5			1			128	106	1	2		2			111	0.472	

\* p-value is from Cochran-Mantel-Haenzel test

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Reviewer's Comment: There were no statistically significant differences in SIRS scores between the two treatment groups at either end of treatment or follow-up.

Microbiological Results: The following table presents the eradication rate for each pathogen seen in the pre-therapy culture for the patient population which was bacteriologically evaluable at follow-up.

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**Table 14**  
**Bacteriological Eradication Rate for Each Pathogen at Follow-up**  
**Per Protocol Bacteriological Population at Follow-up**

Organism Classification	Treatment					
	Mupirocin Calcium Cream			Cephalexin		
	Prelim	Follow-up	Erad Rate (%)	Prelim	Follow-up	Erad Rate (%)
<b>Gram-positive aerobes</b>						
<i>Bacillus polymyxa</i>	0	0		1	0	100
<i>Bacillus species</i>	0	0		1	0	100
<i>Enterococcus</i>	0	0		2	0	100
<i>Staphylococcus aureus</i>	38	0	100	21	0	100
<i>Streptococcus</i> Group A	9	0	100	2	0	100
<i>Streptococcus</i> Group B	2	0	100	2	0	100
<i>Streptococcus</i> Group C	1	0	100	0	0	
<i>Streptococcus</i> Group G	1	0	100	1	0	100
<b>Gram-negative aerobes</b>						
<i>Acinetobacter baumannii</i>	0	0		2	0	100
<i>Acinetobacter lwoffii</i>	3	0	100	0	0	100
<i>Acinetobacter junii</i>	1	0	100	0	0	
<i>johnsonii</i>						
<i>Acinetobacter species</i>	0	0		1	0	100
<i>Agrobacterium radiobacter</i>	1	0	100	0	0	
<i>Citrobacter freundii</i>	1	0	100	0	0	
<i>Comamonas species</i>	1	0	100	0	0	
<i>Escherichia coli</i>	0	0		3	0	100
<i>Enterobacter aerogenes</i>	1	0	100	0	0	
<i>Enterobacter agglomerans</i>	0	0		1	0	100
<i>Enterobacter cloacae</i>	0	0		5	0	100
<i>Flavimonas oryzae</i>	1	0	100	0	0	
<i>Klebsiella pneumoniae</i>	0	0		3	0	100
<i>Moraxella phenylpyruvica</i>	0	0		1	0	100
<i>Moraxella species</i>	2	0	100	0	0	
<i>Proteus mirabilis</i>	1	0	100	0	0	
<i>Pseudomonas aeruginosa</i>	0	0		1	0	100
<i>Pseudomonas chloroaphis</i>	1	0	100	0	0	
<i>Pseudomonas fluorescens</i>	2	0	100	0	0	
<i>Pseudomonas putida</i>	0	0		1	0	100
<i>Pseudomonas stutzeri</i>	1	0	100	0	0	
<i>Serratia marcescens</i>	0	0		1	0	100
<i>Stenotrophomonas maltophilia</i>	1	0	100	0	0	
<b>Gram-positive anaerobes</b>						
<i>Peptostreptococcus magnus</i>	0	0		1	0	100
<i>Peptostreptococcus species</i>	0	0		1	0	100
<b>Gram-negative anaerobes</b>						
<i>Prevotella thaeiomicron</i>	0	0		1	0	100
<i>Veillonella species</i>	1	0	100	0	0	

As noted above, there was a relatively low rate of bacteriologic evaluability in this study.

**Reviewer's Comment:** The applicant notes (volume 25, p. 68 of the NDA) that of the ten pathogens listed in the Intent-to-treat patient population as not eradicated by Bactroban, nine were assumed to not be eradicated because data were lacking; not because persistence was established by analysis. Only one pathogen (*Enterobacter taylorae*) was a proven failure on mupirocin. All pathogens in the per protocol patient populations were eradicated. The reviewers are not convinced that all of the pre-therapy isolates are the causative pathogens in the mild infections seen in this study. Since most were isolated infrequently, they will not be considered for inclusion in the labeling.

**Safety:** The applicant reports that 57/195 (29.2%) of patients randomized to Bactroban reported a total of 84 adverse experiences. Similarly, 57/178 (32.0%) of patients randomized to cephalixin reported a total of 74 adverse events. The majority of these events were not related to drug therapy. The following table (volume 25, p. 74, Table 18) presents the adverse events for each drug which were judged to be possibly or probably related to drug therapy.

**Table 15 Adverse experiences (AEs) considered by the investigator to be related or possibly related to treatment in descending order of frequency by mupirocin calcium cream.**

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N = 195)		Cephalixin (N = 178)	
	n	(%)	n	(%)
Headache	6	(3.1)	3	(1.7)
Diarrhea	3	(1.5)	2	(1.1)
Abdominal Pain	2	(1.0)	1	(0.6)
Application site reaction	2	(1.0)	2	(1.1)
Nausea	2	(1.0)	2	(1.1)
Earache	1	(0.5)	0	(---)
Hot flushes	1	(0.5)	0	(---)
Intermenstrual bleeding	1	(0.5)	0	(---)
Pruritus	1	(0.5)	0	(---)
Constipation	0	(---)	1	(0.6)
Dizziness	0	(---)	1	(0.6)
Dyspepsia	0	(---)	1	(0.6)
Infection fungal	0	(---)	1	(0.6)
Insomnia	0	(---)	1	(0.6)
Lacrimation abnormal	0	(---)	1	(0.6)
Lymphadenopathy	0	(---)	1	(0.6)
Moniliasis genital	0	(---)	1	(0.6)
Rash maculo-papular	0	(---)	1	(0.6)
Rhinitis	0	(---)	1	(0.6)
Taste perversion	0	(---)	1	(0.6)
Patients with AEs	16	(8.2)	19	(10.7)

Data Source: Section 13, Table 13.2 and Appendix D, Patient Listing 39

**Reviewer's Comment:** The case report tabulations (and case report forms where indicated) have been reviewed to assess whether the judgements of the investigators concerning the relationship of the drugs to the adverse reactions seen are accurate. Of the 84 reactions seen in the Bactroban group, the reviewers have found those listed in the following table to be probably or possibly associated with Bactroban therapy. It should be noted that systemic subjective reactions (headache, nausea, abdominal pain) have not been changed by the reviewers.

Table 16 (n = 195)

<u>Adverse Events</u>	<u>n</u>	<u>(%)</u>
Headache	6	(3.1)
Burning	2	(1.0)
Nausea	2	(1.0)
Pruritus	2	(1.0)
Rash	2	(1.0)
Abdominal Pain	<u>2</u>	<u>(1.0)</u>
	16	(8.2)

In summary the adverse events seen in this study were not serious or unusual. The safety of the use of Bactroban Cream in the small infected lesions seen in this study was satisfactory.

Four patients in the Bactroban group withdrew from the study because of 6 adverse reactions. These were: fever (1), abdominal pain (1), earache (1), pruritus (1), rash due to impetigo (1) and respiratory distress (1).

**Conclusions:** Study 129B is acceptable as one study which demonstrates the safety and effectiveness of Bactroban Cream in the treatment of secondarily infected traumatic skin lesions. Bactroban was clinically and microbiologically equivalent to cephalexin.

It is interesting that the oral medication, which might have been presumed to produce more (or more serious) adverse effects than a topical medication did not appear to be less safe than Bactroban. Over half of the infections (38) in the Bactroban group were due to *S. aureus*, with the remainder spread among various pathogens. There were 9 infections due to Group A streptococcus (*Streptococcus pyogenes*).

C. **Study Title:** A Comparative Study of the Efficacy and Safety of Mupirocin Calcium Cream and Cephalexin in the Treatment of Secondarily Infected Eczema (Study No. BRL 4910F/130).

**Reviewer's Note:** This study was prematurely terminated when the sponsor elected to perform two pivotal studies in infected traumatic skin lesions. This application does not request approval for the indication of

The safety data which have been presented will be reviewed. The available efficacy results will be summarized, but detailed description of the protocol effectiveness parameters will be omitted.

**Investigators:** This was a multi-center study conducted at 14 independent sites using a common protocol. The following presentation lists the clinical investigators and the intent-to-treat (ITT) patient enrollment for each treatment arm. The presentation also includes the number of patients who were clinically evaluable per protocol at FU (CLIN) and/or bacteriologically (BACT) evaluable per protocol at the follow-up visit (Mup=Bactroban:Ceph=Cephalexin).

<u>Study Center Number/ Investigator/Location</u>	<u>ITT</u>		<u>CLIN</u>		<u>MICRO</u>	
	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>
001 Stephen Kraus, M.D. 3003 Rivermeade Drive Atlanta, GA	3	2	2	1	0	0
002 Adelaide Hebert, M.D. U Texas Medical School Houston, TX	2	3	2	0	0	0
003 Toivo Rist, M.D. Dermatology Assoc. Knoxville, TN	18	17	10	9	0	0
004 Jay Grossman, M.D. U C San Diego San Diego, CA	2	1	2	0	0	0
005 Leslie Capin, M.D. Aurora Skin Care Aurora, CO	8	7	3	3	0	0
006 Lawrence Parish, M.D. Paddington Testing Co. Philadelphia, PA	16	17	3	3	0	0
007 Mark Weinstein, M.D. Volunteers in Pharm. San Antonio, TX	8	6	2	2	0	0
009 Herbert Moss, M.D. Jackson Foundation Madison, WI	2	2	0	0	0	0

<u>Study Center Number/ Investigator/Location</u>	<u>ITT</u>		<u>CLIN</u>		<u>BACT</u>	
	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>	<u>Mup</u>	<u>Ceph</u>
011 David Crosby, M.D. MCW Clinic Milwaukee, WI	2	0	0	0	0	0
013 Virginia Sulica, M.D. Brenda Berberian, M.D. Georgetown U. Medical Center Washington, D.C.	12	12	4	3	0	0
014 George Nahass, M.D. Rick Barbarash, Pharm.D. St. Louis U. Medical Center St. Louis, MO	0	2	0	0	0	0
015 Samuel McLinen, M.D. Scottsdale Pediatric Center Scottsdale, AZ	3	2	1	1	0	0
016 Richard Pellegrino One Mercy Lane Hot Springs, AR	6	5	0	0	0	0
018 Scott Clark, M.D. Longmont Clinic Longmont, CO	0	1	0	0	0	0
TOTAL	82	77	29	22	0	0

Study Dates: September 13, 1994 - April 28, 1995

Study Objectives: The following is taken directly from volume 30, p. 10 of the NDA:

1. To compare the efficacy, safety and tolerance of mupirocin calcium cream with oral cephalixin in the treatment of patients with secondarily infected eczema.
2. To compare the strain of *Staphylococcus aureus* on the skin with that colonizing the nasal mucosa and to correlate the skin bacterial load of *S. aureus* post-therapy with nasal carriage status.
3. To pharmacoeconomically compare the direct medical resources utilized in the treatment of patients with secondarily infected eczema.

Method:

1. Study design: This was a multicenter, randomized, double-blind, double-dummy parallel-group comparison of the safety and effectiveness of Bactroban Cream and oral cephalixin in the treatment of patients with secondarily infected eczema. A total of 159 patients were randomized to receive study medication (82 Bactroban, 77 cephalixin).

2. Inclusion criteria: The following is taken directly from volume 30, p. 23 of the NDA:

- was 8 years of age or older and weighed > 40 kilograms (88 pounds) and the patient/parent/legal guardian was willing to comply with the protocol.
- had secondarily infected eczema.
- had a Skin Infection Rating Scale (SIRS) score of at least 8.
- had provided written informed consent: Patients under 18 years of age must have had written informed consent from a parent or legal guardian.
- had a negative urine pregnancy test result if a female of childbearing potential.

3. Exclusion criteria: The following is taken directly from volume 30, pp. 23-24 of the NDA:

- had demonstrated a previous hypersensitivity reaction to penicillins, cephalosporins, other  $\beta$ -lactam antibiotics, or mupirocin or any component of the drug.
- had a bacterial skin infection which, due to depth, severity, or extent could not be appropriately treated with a topical antibiotic.
- had received a systemic antibacterial or steroid, or had applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the infected area, or used soap containing an antibacterial agent within 24 hours prior to entering the study.
- had a serious underlying disease.
- was pregnant, breast feeding, or planning a pregnancy during the study.
- had used an investigational drug within 30 days prior to entering this study.
- had previously been enrolled in this study.

4. Dosage and duration of therapy: In order to assure the blinding of the study, a "double-dummy" design was used. Patients received either calcium mupirocin cream 2% (Bactroban) applied 3 times daily plus a placebo for oral cephalexin 4 times daily, or oral cephalexin 4 times daily plus a placebo for Bactroban cream applied 3 times daily.

The treatments continued for 10 days, even if the infection was fully healed. If the infection failed to respond, the investigator had the option of discontinuing the patient. A patient must have received at least 3 days of therapy to be considered evaluable.

Patient evaluations were made at baseline, at day 3-5 of therapy, post therapy (2-3 days after the last dose of medication) and at follow-up (7-9 days after the last dose of medication).

Drug application/dosing was done by the patient or guardian (this was an outpatient study), according to instructions by the investigator. For the topical application of the study drug, the patient/guardian was instructed to clean the wound with warm water and a non-antibacterial soap prior to applying the medication/placebo.

The use of a gauze or bandage was permitted. Use of all other topical agents was prohibited during therapy and for 7 days after therapy or until the follow-up evaluation.

5. Effectiveness Parameters: The effectiveness parameters will not be described in detail. However, they were in general quite similar to those used for the pivotal secondarily infected wounds studies. These included:
- a. Clinical response at end of therapy (success/failure/unable to determine)
  - b. Clinical response at follow-up (persistent success/recurrence) unable to determine)
  - c. Bacteriological response at end of therapy (eradication/improvement/colonization/super-infection/failure/unable to determine)
  - d. Bacteriological response at follow-up (persistent eradication/persistent improvement/colonization/reinfection/relapse/unable to determine)
6. Safety evaluation: The incidence of adverse experiences was compared between the two treatment groups.

**Results:**

Demographics: The following table (volume 30, p. 46, Table 9) summarizes the demographics for the Intent-to-Treat and Per Protocol at end of treatment populations who were clinically evaluable.

Table 1 Demographic characteristics of all randomized patients, as well as those in the per protocol analyses

Demographic Characteristics	Intent-to-Treat (ITT)				Per-Protocol (PP)			
	Mupirocin Calcium Cream (N = 82)		Cephalexin (N = 77)		Mupirocin Calcium Cream (N = 44)		Cephalexin (N = 38)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Sex</b>								
Male	39	(47.6)	48	(62.3)	19	(47.1)	23	(60.5)
Female	43	(52.4)	29	(37.7)	25	(52.9)	15	(39.5)
<b>Age (years)</b>								
2 - 11	4	(4.9)	4	(5.2)	3	(17.6)	0	
12 - 16	3	(3.7)	4	(5.2)	2	(5.9)	6	(15.8)
17 - 65	59	(72.0)	54	(70.1)	33	(47.1)	24	(63.2)
> 65	16	(19.5)	15	(19.5)	6	(9.8)	8	(21.1)
Mean $\pm$ SEM	41.5 $\pm$ 20.2		44.0 $\pm$ 20.0		37.6 $\pm$ 2.92		42.6 $\pm$ 3.43	
Range								
<b>Race</b>								
Caucasian	56	(68.3)	57	(74.0)	34	(77.3)	31	(81.6)
Black	15	(18.3)	15	(19.5)	5	(11.4)	5	(13.2)
Oriental	5	(6.1)	2	(2.6)	2	(4.5)	1	(2.6)
Hispanic	5	(6.1)	3	(3.9)	3	(6.8)	1	(2.6)
Other	1	(1.2)	0		0		0	

Data Source: Section 11.1, Table 11 and Appendix B, Patient Listing 6A. Cross reference ISS Appendix B

Eczema history: The following table (volume 30, p. 47, Table 10) describes the location and history of eczema in the Intent-to-Treat and Per Protocol at end of treatment populations who were clinically evaluable.

**Table 2 Eczema history of all randomized patients**

Disease Characteristics	Intent-to-Treat (ITT)				Per-Protocol (PP)			
	Mupirocin Calcium Cream (N = 82)		Cephalexin (N = 77)		Mupirocin Calcium Cream (N = 44)		Cephalexin (N = 38)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Duration of Eczema (yrs.)</b>								
< 1	29	(35.4)	32	(41.6)	16	(36.4)	17	(44.7)
1 to 5	32	(39.0)	24	(31.2)	19	(43.2)	13	(34.2)
> 5	21	(25.6)	21	(27.3)	9	(20.5)	8	(21.1)
<b>Site of Wound</b>								
Face, neck	12	(14.6)	16	(20.8)	11	(25.0)	10	(26.3)
Anterior trunk	7	(8.5)	3	(3.9)	3	(6.8)	1	(2.6)
Arms	7	(8.5)	5	(6.5)	3	(6.8)	2	(5.3)
Forearms	6	(7.3)	7	(9.1)	2	(4.5)	5	(13.2)
Palms	9	(11.0)	7	(9.1)	6	(13.6)	4	(10.5)
Thighs	2	(2.4)	1	(1.3)	1	(2.3)	0	----
Knees	1	(1.2)	1	(1.3)	0	----	0	----
Legs	12	(14.6)	12	(15.6)	5	(11.4)	7	(18.4)
Feet (dorsal)	9	(11.0)	7	(9.1)	6	(13.6)	4	(10.5)
Scalp, neck	2	(2.4)	4	(5.2)	1	(2.3)	1	(2.6)
Back	2	(2.4)	2	(2.6)	1	(2.3)	1	(2.6)
Buttocks	1	(1.2)	0	----	0	----	0	----
Elbows	1	(1.2)	1	(1.3)	0	----	0	----
Hand (dorsal)	11	(13.4)	10	(13.0)	5	(11.4)	3	(7.9)
Soles	0	----	1	(1.3)	0	----	0	----

Data Source: Section 11.1, Tables 12A and 12C; Appendix B, Patient Listing 8A

Patient Withdrawals: The following table gives the reasons for withdrawal of patients from the study.

**Table 3** The number (%) of randomized patients who completed the study or were withdrawn by the reason for study withdrawal

Study Conclusion Reason	Mupirocin Calcium (N = 82)		Cephalexin (N = 77)	
	N	(%)	N	(%)
COMPLETED STUDY*	69	(84.1)	56	(72.7)
Withdrawal Reason				
Adverse Experiences	3	(3.7)	5	(6.5)
Insufficient Therapeutic Effect	0		6	(7.8)
Deviation from Protocol	5	(6.1)	3	(3.9)
Lost to Follow-up	6	(4.9)	4	(7.8)
Other Reasons	1	(1.2)	1	(1.3)
TOTAL WITHDRAWN	13	(15.8)	21	(27.3)

\*A patient was considered to have completed the study if he/she satisfied all entry criteria, completed 10 days of double-blind therapy and returned for end of therapy and follow-up visits.

**Reviewer's Comment:** The withdrawals due to adverse reactions will be discussed in the safety summary below.

**Effectiveness Parameters:** The efficacy results for this abbreviated study have not been critically examined by the reviewers. The applicant has provided the following tables summarizing their evaluation of the clinical results.

a. Clinical response at end of therapy (volume 30, p. 54, Table 5):

**Table 4 Clinical response at end of therapy (per protocol clinical population)**

Clinical Response	Mupirocin Calcium Cream		Cephalexin		95% Confidence Interval		p-value <sup>[1]</sup>
	n/N*	(%)	n/N*	(%)			
Clinical Success	39/44	(88.6)	31/38	(81.6)	-8.4%	22.5%	0.2852
Clinical Failure	5/44	(11.4)	7/38	(18.4)			

[1] p-value is based on the categorical model with effects for treatment and site.

\*n = number of patients in the per protocol clinical population at end of therapy who were clinical successes or failures, N = total number of patients in the per protocol clinical population at end of therapy, n/N = %

Data Source: Appendix C, Patient Listing 4

b. Clinical response at follow-up (volume 30, p. 118, Table 20B):

**Table 5 Clinical response at Follow-up (Per Protocol Clinical Population)**

Clinical Response	Mupirocin Calcium Cream (N = 33)		Cephalexin (N = 24)		95% Confidence Interval		p-value
	N	(%)	N	(%)			
Clinical Success	33	(100.0)	24	(100.0)	(0.08, 0.08)		
Clinical Recurrence	0		0				

Reviewer's Comment: It should be noted that the failures which are seen at end of therapy (Table 4) have not been brought forward to the follow-up evaluations (Table 5). In addition, the numbers of clinically evaluable patients at follow-up in Table 5 do not agree with the numbers which are arrived at by totaling the numbers of clinically evaluable patients per investigator presented by the applicant. Those totals are 29 for mupirocin and 22 for cephalixin.

c. Bacteriological response at end of therapy (volume 30, p. 125, Table 24):

**Table 6 Bacteriological Response at End of Therapy (Per Protocol Bacteriologically Evaluable Population)**

Clinical Response	Mupirocin		Cephalexin	
	Calcium Cream (N = 2)		(N = 1)	
	N	(%)	N	(%)
SUCCESS	1	(50.0)	0	
Eradication	1	(50.0)	0	
Improvement	0		0	
Colonization	0		0	
FAILURE	1	(50.0)	1	(100.0)
Superinfection	1	(50.0)	0	
Failure	0		1	(100.0)

d. Bacteriological response at follow-up: There were no bacteriologically evaluable patients at follow-up.

**Safety:** The applicant reports that 15/82 (18.3%) of patients randomized to Bactroban reported a total of 28 adverse events. Similarly, 18/77 (23.4%) of patients randomized to cephalixin reported a total of 27 adverse events. The majority of these events were not related to study drug therapy. The following table presents the adverse events for each drug which were judged to be possibly or probably related to drug therapy by the reviewers. Once again, subjective reactions are attributed to drug treatment.

**Table 7 Adverse experiences (AEs) considered by the reviewers to be related or possibly related to treatment for study 130.**

AE	Mupirocin Calcium Cream (N = 82)		Cephalexin- (N = 77)	
	n	(%)	n	(%)
Nausea	4	(4.9)	3	(3.8)
Headache	3	(3.6)	0	(0.0)
Application site rx	3	(3.6)	0	(0.0)
Pruritis	2	(2.4)	0	(0.0)
Abdominal pain/cramps	1	(1.2)	1	(1.2)
Bleeding secondary to eczema	1	(1.2)	0	(0.0)
Pain secondary to eczema	1	(1.2)	0	(0.0)
Hives	1	(1.2)	0	(0.0)
Skin dryness	1	(1.2)	0	(0.0)
Rash	1	(1.2)	0	(0.0)
Flushed skin	0	(0.0)	1	(1.2)
Exacerbation of disease	0	(0.0)	10	(13.0)
Acneiform eruption	0	(0.0)	1	(1.2)
	18	(21.9)	16	(20.8)

**Reviewers Comment:** The adverse reactions seen in the eczema patients were more numerous than those seen in the secondarily infected traumatic wound group. The most striking entry is the number of patients whose eczema was exacerbated during cephalixin therapy (10/77 = 13%). The Bactroban reactions seen were not serious or unusual. Three patients in the Bactroban group withdrew from the study because of a total of 7 adverse reactions. These were: application site reaction (1), fever (1), otitis media (1), upper respiratory tract infection (1), pruritus (1), dry skin (1) and urticaria (1).

**Conclusions:** This study contributes useful additional safety information concerning the use of Bactroban in diseased skin. The results do not indicate that cephalixin is a suitable control drug for the study of infected eczema, due to the relatively high rate of exacerbation of disease in the cephalixin group.

**D. Efficacy Summary:** Studies 129A and 129B provide convincing evidence of the safety and effectiveness of Bactroban Cream in the treatment of secondarily infected traumatic skin lesions due to *Staphylococcus aureus* and *Streptococcus pyogenes*.

These studies were performed under identical protocols with different sets of investigators. In both studies, Bactroban Cream applied 3 times daily was highly effective (greater than a 90% cure rate) and statistically equivalent in effectiveness to oral cephalexin given 4 times daily. The treatment regimens were both well tolerated, with minor adverse events reported at a low frequency. Adult and pediatric patients were represented, through there were relatively few patients below the age of 2 years.

Both treatments were effective against the pre-therapy pathogens as assessed at the follow-up visit, although there were adequate numbers of only two: *Staphylococcus aureus* and *Streptococcus pyogenes*. The cure rate for *Staphylococcus aureus* in studies 129A and 129B combined was 62/64 (96.8%). The cure rate for *Streptococcus pyogenes* in the combined studies was 11/11 (100%).

In the pediatric population, there were 93 pediatric patients aged 2 weeks to 16 years enrolled per protocol in the combined studies, though only 3 were less than 2 years of age in the Bactroban Cream population. One of the 3 children was 2 weeks of age; the other 2 were one year old.

The clinical success rates for the clinically evaluable patients at FU in the two studies were as follows:

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**Clinical response at follow-up for Study 129A**

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Clinical Response	Mupirocin Calcium Cream (N = 103)		Cephalexin (N = 104)		95% Confidence Interval
	N	(%)	N	(%)	
Persistent Clinical Success	97	(94.2)	94	(90.3)	(-4.4, 12.0)
Recurrence	0	(0.0)	1	(1.0)	
Clinical Failure at EOT	6	(5.8)	9	(8.6)	

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**Clinical response at follow-up for Study 129B**

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Clinical Response	Mupirocin Calcium Cream (N = 128)		Cephalexin (N = 115)		95% Confidence Interval
	n	(%)	n	(%)	
Persistent Clinical Success	125	(97.6)	110	(95.6)	(-3.4, 7.4)
Recurrence	1	(0.8)	2	(1.8)	
Clinical Failure at EOT	2	(1.5)	3	(2.6)	

It is noted that the clinical and statistical reviewers had slightly different numbers of patients at follow-up because the statistical reviewer included the patients who missed the end-of-therapy evaluability window, while the clinical reviewers brought forward some failures from the end of treatment. These differences do not change the outcome in terms of approvability of the NDA.

**II. Review of Safety Studies (Absorption, Irritancy and Sensitization) and Safety Summary**

- A. Study Title:** A Single Blind, Placebo Controlled Study to Assess the Irritancy and Sensitization Potential of Mupirocin 2% Cream After Repeated Topical Application to Healthy Human Skin (Study No. 4910F/109/FR4/001/AMOS).

**Investigator:** H.E. Amos, Ph.D.  
Pharmaco: LSR Ltd.  
Chelmsford, Essex  
United Kingdom

The C.V. for Dr. Amos has been reviewed and he is well qualified to conduct this study.

**Study Dates:** May 14 - October 27, 1993

**Study Objectives:** The following is taken directly from volume 16, p. 13 of the NDA:

**OBJECTIVES:** 1) To assess the primary dermal irritancy potential of mupirocin 2% cream compared to placebo cream and mupirocin 2% ointment following repeat open applications to normal skin. 2) To assess the dermal irritancy potential of mupirocin 2% cream compared to placebo cream and mupirocin 2% ointment following repeat semi-occluded and occluded applications for increasing periods to normal skin. 3) To investigate the dermal irritancy and sensitization potential of mupirocin 2% cream and placebo cream following repeat occluded applications to normal skin.

**Method:**

1. **Study design:** This was a double-blind (subject and evaluator blind) randomized, paired-comparison study in which each test subject served as his own control. The study was performed in three stages: the first two stages were pilot studies in groups of 10 subjects each, with the test medications being mupirocin cream 2%, mupirocin cream vehicle and mupirocin ointment 2%. The third stage was performed in 102 subjects, comparing mupirocin cream 2% and its vehicle.

2. Inclusion criteria: The following is taken directly from volume 16, p. 24 of the NDA:

Men and women aged between 18 and 60 years who had given written informed consent to participate in the study.

No abnormality on clinical examination performed within 20 days of the start of study treatment (unless the Principal Investigator considered any associated condition to be clinically irrelevant).

Normal laboratory values for clinical chemistry, hematology and urinalysis performed within 20 days of starting study treatment (unless the Principal Investigator considered an abnormality to be clinically irrelevant).

No clinically important abnormality in ECG considered relevant to the conduct of the study by the Principal Investigator.

3. Exclusion criteria: The following is taken directly from volume 16, pp. 24-25 of the NDA.

Female subjects of child bearing potential who were sexually active and not taking reliable contraceptive precautions.

Female subjects who were pregnant or breast feeding.

Subjects receiving any other form of drug therapy or medication on a regular basis (unless considered irrelevant to outcome of the study by the Principal Investigator).

Subjects who had taken prescription medication within the last 7 days including over-the-counter remedies within 48 hours before the first dosing day (except oral contraceptives or HRT), unless the Principal Investigator considered them to be clinically irrelevant, and unlikely to affect the outcome of the study.

History of drug or alcohol abuse (defined as follows: by a positive urine drug screen for undeclared drugs of abuse; or an average daily intake of alcohol greater than 4 units and maximum weekly intake of over 21 units for males and 14 units for females).

Participated in a trial with a new chemical entity within 4 months before the start of study treatment.

Participated in a trial with an investigational drug or product within one month before the start of study treatment.

Definite or suspected personal history or family history of adverse reactions or hypersensitivity to the study drug, or to drugs with a similar chemical structure, unless appropriate investigation had shown the subject to be clear of risk.

Skin diseases of any type except mild acne.

Contact sensitivity to Elastoplast or similar materials.

History of skin eruptions to food or drugs.

History of asthma or atopy.

Subjects who had received an immunization within one month prior to the start of study treatment.

4. Method: The following summary is taken directly from volume 16, pp. 18-19 of the NDA (0.1 mL applications of the test medications were made to 2 x 2 cm skin areas.)

Stage 1: Ten subjects each received single daily applications for five days comprising mupirocin 2% cream, mupirocin placebo cream and mupirocin 2% ointment. Each treatment was applied concomitantly to separate sites on the forearm and left in-situ for five hours. Residual cream was removed after five hours and visual assessments for irritancy performed at 6 hr and 24 hr after each application.

Stage 2: Ten subjects each received two semi-occluded patch applications (5 hr and 18 hr duration, respectively), followed by two occluded applications (2 x 23 hr duration each) over a total period of 72 hours. Treatment comprised repeat applications of mupirocin 2% cream, mupirocin placebo cream and mupirocin 2% ointment, applied concomitantly under a separate dressing to the upper arm, over the following time periods: 0-5 hr, 6-24 hr, 25-48 hr and 49-72 hr. Visual assessments for irritancy were performed one hour after removal of each patch.

Stage 3: One hundred and two subjects received nine separate patch applications of mupirocin 2% cream and placebo cream base, concomitantly, over a period of 22 days. Applications were made on days 1, 3, 5, 8, 10, 12, 15, 17 and 19, to the upper back and occluded for 48 to 72 hours.

A challenge was performed two weeks later on day 36, with fresh applications of active and placebo cream applied to remove sites and occluded for 24 hours.

Visual assessments for irritancy was made at least 15 minutes after patch removal on days 3 to 22 and following challenge for contact sensitivity reactions on day 37 and 24 hours later on days 38 and 39, respectively.

5. Safety assessments: The following rating scales were used in grading irritancy and sensitization reactions.

#### Irritancy Scale

0	-	No apparent cutaneous involvement.
½	-	Faint, barely perceptible erythema or slight dryness (glazed appearance).
1	-	Faint but definite erythema, no eruptions or broken skin <u>or</u> no erythema but definite dryness; may have epidermal fissuring.
2	-	Moderate erythema, may have a very few papules <u>or</u> deep fissures, moderate-to-severe erythema in the cracks.
2 ½	-	Moderate erythema with barely perceptible edema <u>or</u> severe erythema not involving a significant portion of the patch (halo effect around the edges), may have a few papules <u>or</u> moderate-to-severe erythema.
3	-	Severe erythema (beet redness), may have generalized papules <u>or</u> moderate-to-severe erythema with isolated eschar formations or vesicles.
3 ½	-	Moderate-to-severe erythema with moderate edema (confined to patch area) <u>or</u> moderate-to-severe erythema with isolated eschar formations or vesicles.

- 4 - Generalized vesicles or eschar formations or moderate-to-severe erythema and/or edema extending beyond the area of the patch.

Sensitization Scale

- 0 - No visible reaction. This score would include superficial skin responses such as glazing, peeling, cracking.
- 1 - Mild erythematous reaction. Faint pink to definite pink.
- \*1E - Mild erythematous reaction with papules and/or edema.
- 2 - Moderate erythematous reaction. Definite pink to red erythema (similar to sunburn).
- \*2E - Moderate erythematous reaction with edema and/or papules.
- 3 - Strong erythematous reaction. Beet red.
- \*3E - Strong erythematous reaction with marked edema, papules and/or few vesicles.
- 4 - Severe reaction with erythema, edema, papules and vesicles (may be evidence of weeping).
- 5 - Bullous reaction.
- S - Reaction spread beyond patch size.
- A - Adhesive reaction to tape

Note: Erythema, papules, edema and vesicles are judged to be present if they involve 25% or more of the patch site.

\* If papules are present then add P i.e. 1EP. If vesicles then add V i.e. 1EV.

Results:

Demographics: One hundred twelve healthy volunteers participated in the study. The same 10 subjects participated in Stages 1 and 2 although they were not included in the 102 subjects in Stage 3. There were 75 females and 37 males in the group, aged \_\_\_\_\_ years (mean age 35 years).

Stage 1: There were no reactions in Stage 1.

Stage 2: Six of 10 subjects responded to mupirocin cream 2%, 8/10 responded to mupirocin ointment 2% and 7/10 responded to cream vehicle. All responses were 1 on the irritancy scale (or less) except for 2/10 scores of 1.5 for the mupirocin ointment 2% and vehicle cream applications.

Stage 3: This portion of the protocol corresponds to the standard sensitization study which is often used in support of the safety of topical drug products. While the applicant has reported irritancy scores from the initial (or "induction") part of the study, the nine patch applications made are fewer than the 15 made over a 3 week period as in the standard irritation study.

In the induction phase, 76/102 subjects (74.5%) were classed as "responders", meaning they had a score of at least one at any observation. There were only 3 scores of two, however. The following table, which is adapted from Table 3, volume 16, p. 45 of the NDA, presents these data.

Table 1 - Irritancy Scores by Treatment  
(N = 102)

Treatment	0	1	2	Mean
Mupirocin Cream	46	54	2	0.57
Vehicle Cream	45	56	1	0.57

In the sensitization ("challenge") phase, fresh applications of the test materials were made to previously unpatched sites 2 weeks after the induction phase was completed. Assessment of sensitization was made immediately upon removal of the challenge patch and 24 and 48 hours after removal. Ninety-four of the original 102 subjects completed this phase. Twenty-five of the 94 were classified as "responders", meaning they had a score of at least one at any observation, although there were no scores greater than one.

The following tables are adapted from tables 8 and 9, volume 16, p. 46 of the NDA.

Table 2 - Number of Responders by Treatment

Both Treatments	Mupirocin Cream Only	Vehicle Cream Only
7/94 = 7.4%	10/94 = 10.6%	8/94 = 8.5%

Table 3 - Maximum score by Treatment

Treatment	0	1	Mean
Mupirocin Cream	77	17	0.18
Vehicle Cream	79	15	0.16

Adverse Events: There were 8 subjects who withdrew from the study during Stage 3 prior to the challenge application due to adverse events. One subject had a severe application site reaction after the patch application on Day 5. The reaction was to both the active and the vehicle patches and was considered to be related to medication application. Two other subjects had irritancy scores of 2 and were withdrawn from the induction phase of the study, but successfully completed the challenge phase. The other withdrawals were judged not to be related to medication application. These reactions were: conjunctivitis, dizziness, cystitis, exacerbation of hypertension, and arthralgia and headache in one subject.

There were 37 other adverse events reported, most of which had no connection to medication application (headache, injury, respiratory disorders, etc). There was one subject who developed a rash on her neck which was possibly treatment related.

**Conclusions:** This study provides adequate evidence that Bactroban Cream is not unusually irritating or sensitizing. The irritancy section of this protocol did not utilize as many test patches as is seen in the standard irritancy study, but the results of Stage 2 of the study, in which the cream was not more irritating than the marketed ointment formulation, along with the results of Stage 3 provide sufficient evidence of the relative lack of irritancy potential for the cream.

In addition, the low scores seen in the sensitization portion of the protocol do not indicate severe sensitization. The applicant presents the possibility that these reactions were due more to irritancy than to sensitization and this theory is probably correct. The one case of sensitization which seems likely is in the subject who was withdrawn from the study because of a severe reaction after the Day 5 patch application.

B. **Study Title:** An Open-Label Study of Percutaneous Absorption of Calcium Mupirocin Cream Applied to Skin Lesions of Children and Adults (Study No. 142).

**Investigators:** Marie Uberti-Benz, M.D.  
Presbyterian Medical Center of Philadelphia  
Philadelphia, PA

Paul Honig, M.D.  
Children's Hospital of Philadelphia  
Philadelphia, PA

Jerry Herron, M.D.  
Arkansas Research Medical Testing Center  
Little Rock, AR

**Study Dates:** October 27, 1995 - January 28, 1996

**Study Objectives:** The following is taken directly from volume 11, p. 25 of the NDA:

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.

**Method:** The method will not be described in detail. The reader is referred to Dr. Ajayi's biopharmaceutics review dated April 1, 1997.

Briefly, this was a prospective, uncontrolled, open-label study. The test subjects applied Bactroban Cream to skin lesions three times daily for 5 days and once on Day 6. The subjects were males and females between \_\_\_\_\_ years or \_\_\_\_\_ years who had a skin lesion of

one of the following types: laceration or sutured wound (size  $\leq 10$  cm in length); abrasion (size  $\leq 100$  cm<sup>2</sup>); atopic dermatitis (size  $\leq 100$  cm<sup>2</sup>); or stasis dermatitis (size  $\leq 100$  cm<sup>2</sup>).

**Results:**

Demographics: There were 29 subjects entered into the study. The following table (volume 11, p. 30, Table 10.1) summarizes the demographics of the group.

Group	Parameter	Age (years)	Height (cm)	Weight (kg)	Body Surface Area (BSA) (m <sup>2</sup> )
Adults	N	19	19	19	19
	Mean	41	173	72.4	1.86
	SD	8.8	9.6	10.20	0.166
	Range				
Children	N	10	10	10	10
	Mean	8	132	28.5	1.02
	SD	3.6	22.1	8.38	0.235
	Range				

Additional demographics and wound conditions are as follows:

Group	Sex		Race			Condition*				
	M	F	White	Black	Other	Lac.	Ab.	A.D.	Ecz.	S.D.
Adults	14	5	11	7	1	5	5	2	6	1
Children	5	5	6	3	1	1	2	5	2	0

\*Lac. = laceration, Ab. = abrasion, A.D. = atopic dermatitis, Ecz. = eczema, S.D. = stasis dermatitis

Safety Results: Two of the children incurred application site reactions (burning) during the study. No treatment was necessary for these occurrences.

C. Safety Summary: The safety data submitted in support of this NDA indicate that Bactroban Cream is safe for use in secondarily infected skin lesions.

In the two pivotal studies in infected skin lesions (129A and 129B), the adverse reactions seen in both test groups (Bactroban and cephalixin) were relatively mild and were not unusual. It is somewhat surprising that there were so few reactions in the cephalixin group, as it would seem likely that a systemic medication would be more toxic than a topical one in similar patient groups. In any event the total adverse reaction rates for the two studies, if limited to those judged by the investigator to be possibly or probably related to treatment are for Bactroban 26/339 = 7.7% and for cephalixin 32/327 = 9.8%. The most frequent reaction in the Bactroban group was headache (7) and in the cephalixin group it was diarrhea (also 7).

The reviewer's evaluation of the adverse experiences in the Bactroban group found 28/339 = 8.3% reactions probably or possibly related to treatment.

In the supportive safety studies, there were more adverse events seen in the infected eczema study, which was prematurely terminated. This can probably be attributed to the fragility of the disease site in the eczema patients. The relatively high rate (13%) of disease exacerbation in the cephalexin group brings into question the suitability of this drug as a positive control in studies of infected eczema.

Bactroban Cream is not expected to be unusually irritating or sensitizing in normal use.

### III. Review of Labeling

The following is the recommended package insert for use with Bactroban Cream.

Redacted

4

pages of trade

secret and/or

confidential

commercial

information

Reviewer's Comment: It is noted that there are only 3 children below the age of 2 years in the Bactroban test group. The youngest was aged 15 days. All 3 children were clinical successes. It is felt that since there is no significant systemic absorption of Bactroban, and the adverse reactions seen in the clinical trials were not significant, there are no reasons to restrict the use of the drug in younger children. There is also no reason to expect that the efficacy of the drug would change with respect to the age of the patient. It is noted that the primary pathogen for secondarily infected small traumatic lesions would be *Staphylococcus aureus* or *Streptococcus pyogenes* in pediatric patients  $\geq$  3 months of age, whereas in patients less than 3 months of age gram negatives may play a more prominent role. Thus, the reviewers are recommending the use of Bactroban Cream for the treatment of secondarily infected small skin lesions in pediatric patients 3 months of age and older.

IV. Conclusions and Recommendations:

Bactroban Cream 2% is recommended for approval for the indication "treatment of secondarily infected small traumatic skin lesions due to susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*." The applicant also requested inclusion of beta-hemolytic *Streptococcus* in the labeling. The term "beta-hemolytic streptococcus" includes a group of streptococcal organisms that have not been fully identified but merely grouped by their hemolysis reaction. The Division has not been granting organism groups in the label. In addition, there were not sufficient isolates of those pathogens to justify their inclusion in the labeling. In two well-designed, double-blind comparisons of Bactroban Cream applied 3 times daily vs. oral cephalixin used 4 times daily, Bactroban Cream proved to be at least as safe and efficacious as cephalixin. The cure rate for Bactroban Cream was 96% in infected small lacerations, sutured wounds or abrasions, with all pathogens in the per protocol bacteriologically evaluable patients being eradicated. Adverse reactions which could probably or possibly be connected to drug therapy occurred in about 8% of Bactroban Cream patients, and these reactions were not severe or unexpected. Further, there is no indication that Bactroban Cream is unusually irritating or sensitizing.

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David C. Bostwick  
Clinical Reviewer

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Rosemary Roberts, M.D.  
Clinical Team Leader

Orig NDA

HFD-340

HFD-520

HFD-520/Clin/Bostwick *RR 11/5/97*

HFD-520/TLClin/Roberts *RR 11/5/97*

HFD-520/Proj Mgr/Dillon-Parker

HFD-520/Pharm/Peters

HFD-520/Micro/King

HFD-520/Chem/Timper

HFD-240

CONCURRENCE:

HFD-520/ActgDivDir/Chikami

HFD-520/TLClin/Roberts

*RR*  
*11/5/97*

*11/10/97*