CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-788

MEDICAL REVIEW(S)

CLINICAL REVIEW COVER SHEET

NDA 50-788

Mupirocin Ointment, 2%

Sponsor: Clay-Park Labs, Inc,

Bronx, NY 10457

Date of Submission: February 7, 2002

Date CDER Received: February 8, 2002

Date Assigned to Reviewer: February 14, 2002

Date Review Initiated: February 25, 2002

Date Review to Supervisor: August 8, 2002

Ten – Month Deadline: December 7, 2002

The Executive Summary of the Primary Clinical Review

1. Recommendations

1.1 Recommendations on approvability.
This drug may be approved from a clinical perspective. The product was evaluated in a double-blind, controlled clinical study versus Bactroban (mupirocin 2%) Ointment in 602 (ITT) patients with impetigo. In the primary efficacy endpoint, clinical response at follow-up visit, 94% of the Clay-Park Mupirocin Ointment patients were evaluated as successes, vs. 95% of the Bactroban Ointment patients in the per protocol patient population. The adverse events reported for the two treatment groups were similar in frequency and type. The most frequent adverse events related to study medication were dermatologic (application site reaction, pruritus). These events occurred in about 4% of the study population. This drug is safe and effective when used as directed.

1.2. Recommendation on Postmarketing Studies and/or Risk Management Steps when Appropriate.

None.

2. Summary

2.1. Brief Overview of Clinical Program

A. Product name, class, and route of administration.

The product is Mupirocin Ointment, 2%. It is a topical anti-infective for use against impetigo.

B. Indication and population studied.

This product is indicated for the topical treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*.

The product was studied in patients with the stated indication. Since impetigo is typically a disease of children, the patient population in the studies was young, averaging about nine years of age. There were some (15%) patients who were 15 years of age and older.

C. Number of primary safety and efficacy trials.

There was one pivotal efficacy trial performed in support of this NDA, as previously agreed to by the Division. There were also three safety

studies performed: an irritancy study, a sensitization study and an absorption study.

D. Number of patients enrolled in the primary trials

i. Pivotal efficacy trial
Study no: CPL-002
Design: Double-blind, parallel-group, active control
No. subjects (ITT): Mupirocin Ointment 300, Bactroban Ointment 302

ii. Irritancy Study
Study no: KGL 4681
Design: Double-blind, paired-comparison of Mupirocin Ointment, its vehicle, Bactroban Cream, 1% sodium lauryl sulfate and physiological saline
No. subjects: 27

iii. Sensitization study
Study no: KGL 4682
Design: Double-blind, paired comparison of Mupirocin Ointment, its vehicle and Bactroban Cream
No. subjects: 191

iv. Absorption study
Study no: FARMOUS 125/2001
Design: Open-label, randomized, crossover comparison of Mupirocin Ointment and Bactroban Ointment
No. subjects: 24

E. Overall number of patients in the safety database

Mupirocin Ointment: 561
Bactroban Ointment or Cream: 539

2.2. Efficacy

Impetigo is a highly communicable infection, most often seen in preschool-age children. It is generally superficial, beginning with small vesicles which rapidly progress to pustules, which easily rupture. If the infection is untreated, the process may persist and new lesions develop over the course of several weeks. The infection then tends to resolve spontaneously, so impetigo is usually a self-limiting disease. Treatment is indicated to prevent person-to-person transmission and to prevent progression to more serious disease (eg, cellulitis), which may rarely occur if left untreated.

There are two commonly recognized forms of the disease. The first, often identified as bullous impetigo, is usually associated with *S. aureus* infections. The second, simply called impetigo but also known as impetigo contagiosa, is commonly due to *S. pyogenes*. Mixtures of streptococci and *S. aureus* have been isolated from many patients with impetigo contagiosa, but *S. aureus* appears to be subsidiary in this form. The pivotal efficacy study for this NDA was performed primarily in South Africa, with some patients also studied in Puerto Rico. There is no information to indicate that the course of the disease would be different in these areas than in the continental United States.

The effectiveness of the Clay-Park Mupirocin Ointment product is established by a well-controlled, randomized, double-blind comparison to Bactroban Ointment, which is the standard of care for impetigo in this country. The study included a majority of patients in the age group which is most vulnerable to this disease (less than 10 years of age) as well as subjects in older age groups. There were significant numbers of patients with either or both of the pathogens associated with the disease.

The pivotal trial provided for approximately one week of treatment, with the test medications applied three times daily. Evaluations were performed at day 3-5 of treatment, at end of treatment (day 7-9 of the study) and at follow-up (day 12-16 of the study).

The parameters studied included:

a) Skin Infection Rating Scale (SIRS), which evaluated blistering, exudate/pus, crusting, erythema/inflammation and itching/pain on a numerical scale from 0= none to 6= severe.

b) Clinical response at follow-up was the primary efficacy endpoint. A "clinical success" was defined as sufficient resolution of signs and symptoms of infection such that no additional antibiotic therapy was required, as evidenced by a SIRS score ≤ 2 for erythema/inflammation and itching/pain, and ≤ 1 for the other SIRS categories (the total SIRS score must have been at least 8 for study entrance).

c) Clinical response at end of therapy.

d) Bacteriological success, defined as elimination of *S. aureus* and *S. pyogenes* at follow-up and/or end of therapy.

Results were as follows:

a) Clinical response at follow-up

	Mupirocin Ointment		Bactroban Ointment		95% C. I.
Per Protocol					
Success	218/233	(94%)	231/242	(95%)	(-6.4, 2.6)
Modified ITT					
Success	249/279	(89%)	251/279	(90%)	(-6.1, 4.7)

The modified 1TT population had at least one dose of medication, at least one post-baseline visit, and a positive baseline culture.

b) Bacteriological response at follow-up

	Mupirocin Ointment		Bactroban Ointment		95% C. I.
Per Protocol					
Success	228/233	(98%)	237/242	(98%)	(-3.1, 2.9)
Modified ITT					
Success	261/279	(94%)	258/279	(92%)	(-3.5, 5.7)

c) Clinical response at end of therapy

	Mupirocin Ointment		Bactroban Ointment		95% C. I.
Per Protocol					
Success	195/233	(84%)	190/242	(79%)	(-2.3,12.6)
Modified ITT					
Success	224/279	(80%)	213/279	(76%)	(-3.2, 11.1)

d) Bacteriological response at end of therapy

	Mupirocin Ointment		Bactroban Ointment		95% C. I.
Per Protocol					
Success	232/233	(100%)	238/242	(98%)	(-1.2, 2.9)
Modified ITT					
Success	267/279	(96%)	265/279	(95%)	(-3.1, 4.6)

e) Overall SIRS scores at end of therapy and follow-up

	Mupirocin Ointment	Bactroban Ointment	p-value
Per Protocol			
EOT	1.38 ± 2.00	1.40 ± 1.99	0.810
Followup	0.47 ± 1.52	0.38 ± 0.83	0.957
Modified ITT			
EOT	1.63 ± 2.57	1.59 ± 2.20	0.737
Followup	0.73± 2.03	0.67 ± 1.48	0.847

The endpoints used in this study (symptomatology, eradication of the causative pathogen) are appropriate to the evaluation of a medication used in the treatment of impetigo. Since the disease is usually self-limiting, the high success rate is expected. This study establishes that Clay-Park's Mupirocin Ointment is as effective in treating impetigo as is Bactroban Ointment, which is generally considered to be the standard of care for this disorder. There are no unresolved efficacy issues with this product.

2.3. Safety

Safety for the use of Mupirocin Ointment 2% is established by the following:

- Adverse event reports
- A predictive irritancy study (human)
- A predictive sensitization study (human)
- An absorption study (human).

As noted above, there were 561 patients and healthy test subjects exposed to Clay-Park's Mupirocin Ointment during the course of drug development. Exposures included three doses daily of the 2% ointment for seven days to affected skin areas in the pivotal studies; application of 2 grams daily for seven days during the absorption study (the dosed area was occluded for 12 hours daily during this study), for a total mupirocin dose of 280 mg over the seven days; application of 0.1 mL of the ointment to a designated site for 21 consecutive days during the irritation study (the drug was reapplied 15 times during the course of this study); and application of 0.1 mL of the ointment to a designated site for 21 consecutive days during the sensitization study (the drug was reapplied 9 times during the course of this study). The application sites were constantly occluded during the irritation and sensitization studies. There were 279 patients who received at least one dose of Mupirocin Ointment during the pivotal clinical study. The following items were considered during the course of evaluating the safety of this product:

a. Adverse events.

There were 55/300 = 18.3% of patients in the Mupirocin Ointment patient group who experienced adverse events during the pivotal clinical study, vs. 40/302 = 13.2% of patients in the Bactroban Ointment group. The applicant has divided these reactions into two groups: those which were skin related and those which were not. The numbers of patients with skin related reactions were nearly identical between the groups (12 for Mupirocin Ointment and 13 for Bactroban Ointment), while there were 43 patients with non skin related events in the Mupirocin Ointment group vs. 27 in the Bactroban Ointment group. The non skin related events were not classified as being associated with the study drug (they include occurrences such as accidents, fever, pharyngitis, etc.). Discontinuances due to adverse events totaled four for Mupirocin Ointment patients and two for Bactroban Ointment patients.

In the absorption study 4/24 (16.7%) of the test subjects experienced adverse events. Two of these were headache, and the other two skin related reactions. It is noted that the application sites for this study were occluded for twelve hours daily.

In the irritation study, 2/30 subjects who entered the study reported adverse events, but they were judged not to be related to drug therapy. In the sensitization study, three subjects reported headaches, also not related to drug therapy.

b. Predictive irritancy study

This study is designed to produce conditions conducive to irritation in order to determine what the potential of the test products might be to cause irritancy during normal use. Study products are applied continuously and repeatedly under occlusive dressings for 21 days. The results indicate that Mupirocin Ointment, Bactroban Cream and the negative control, physiological saline, produced similar (very low) cumulative irritation scores (total scores 8-18) while the positive control, 0.1% sodium lauryl sulfate, produced a relatively high score (151).

c. Predictive sensitization study

This study examines the potential for the test products to produce allergic reactions under extreme testing conditions. Study products are applied continuously and repeatedly under occlusive dressings for 3 weeks. A two week rest period (no drug application) is observed, followed by challenge of the subject at a naïve (previously unpatched) test site for 48 hours. The results indicate that none of the test products (Mupirocin Ointment, Bactroban

Ointment, Bactoban Cream or the negative control, petroleum jelly) has a potential to produce sensitization reactions.

d. Human absorption study

This study compared systemic exposure produced by seven once daily applications of Mupirocin Ointment and Bactroban Ointment. After the first product was applied for one week, an 8 day washout period was observed, and then the test subject was dosed with the other product in the study. Thus, each subject served as his/her own control. Twenty-three subjects completed the study. The application sites were occluded for 12 hours on each day of drug dosing. The total amount of mupirocin received per subject during each one week dosing period was 280 mg.

The absorption of each drug was measured by the 24-hour urinary excretion of monic acid, the principal metabolite of mupirocin. Results indicated that a mean of 0.29% of the dose of Bactroban Ointment applied was excreted in 24 hours, vs. a mean of 1.29% for Mupirocin Ointment.

The Biopharmaceutics review should be consulted for a complete evaluation of this study. However, a systemic exposure study performed with up to a 250 mg mupirocin dose did not produce any apparent reactions. The 24 hour exposure to mupirocin in the topical study described above averaged 40 mg mupirocin, though much less than that was absorbed.

Other issues which are noted concerning the safety profile of Mupirocin Ointment include:

a. Animal toxicity findings

Clay-Park does not use the same inactive ingredients in their formulation as those used in Bactroban Ointment (the Bactroban formulation contains polyethylene glycol 400 and polyethylene glycol 3350). The excipients for Mupirocin Ointment are as follows:

Ingredient	% W/W
Softisan 378 (hard fat)	[redacted]
Castor Oil	
Propylene glycol Monostearate	[redacted]
Oleyl Alcohol	[redacted]

A dermal irritation study conducted in rabbits indicated that Mupirocin Ointment produced mild to moderate irritation, perhaps due to inclusion of the castor oil. However, the results of the human irritancy study are

satisfactory in that they indicate that Mupirocin Ointment should be no more irritating in human use than a negative control substance (normal saline).

b. Exposure in trials vs. probable marketing exposure.

Exposure in clinical trials is the same as would be expected when the drug is used as directed in the "Dosage and Administration" section of the label.

c. Effect of trial exclusions on safety profile versus expected population for marketed drug.

Exclusions in the patient populace were very small. The population seen in the pivotal clinical trial is the same as would be expected in the general patient populace.

d. Relationship of safety to other drugs available.

See a) Adverse events, above.

2.4. Dosing, Regimen, and Administration

The dosage regimen for this drug was chosen based on the regimen used for the comparator, Bactroban Ointment. It is possible that fewer treatments per day (e.g., two rather than three) would result in the same high level of effectiveness. However, the low adverse reaction rate seen with three times daily dosing establishes that this dosing regimen is satisfactory.

2.5. Drug – Drug Interactions

No studies have been performed concerning the possible interaction of Mupirocin Ointment and other topical medications.

2.6. Special Populations

As noted above, this product is used predominantly in young children, and this is the age group which was studied. The following table, which is adapted from Table 8-25 on page 8-100 of volume 1.10 of the NDA, briefly describes the demographics of the patients studied in the pivotal efficacy study:

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Demographic Characteristics for ITT Subjects

Parameter	Mupirocin Ointment (N=300)	Bactroban Ointment (N=302)	p-value
Gender (n, %)			
Male	148(49%)	144 (48%)	0.793
Female	154(51%)	158 (52%)	
Race (n, %)			
White	12 (4%)	10 (3%)	0.683
Black	174 (58%)	182 (60%)	
Other	114 (38%)	110 (36%)	
Age (years)			
Mean ± Std	9.18 ± 10.01	8.75 ± 9.2	0.926
Min – Max	0.2 - 58.5	0.3 - 54.0	
Number (%) of Subjects			
< 5 yrs	132 (44%)	131 (43%)	
6-10 yrs	88 (29%)	94 (31%)	
11-15 yrs	36 (12%)	39 (13%)	
< 15 yrs	44 (15%)	38 (13%)	

The only remarkable demographic characteristic is the paucity of white patients in the study. Use in the continental U.S. will involve a larger proportion of white patients. There is no information to indicate that the course of impetigo is affected by age, race, or sex, either in this study or in the literature.

This drug will probably be used in a relatively small number of pregnant patients. The pregnancy category for this drug is B.

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Clinical Review

1. Introduction and Background

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

The established and trade names for the product are identical: Mupirocin Ointment, 2%. Mupirocin Ointment is a topical antibiotic intended for the topical treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*. The drug is to be applied to the affected skin area three times daily. Patients who do not show a clinical response in 3 to 5 days are to be reevaluated. The drug may be used in any patient 2 months of age or older.

1.2. State of Armamentarium for Indication

Bactroban (mupirocin) Ointment, which is the comparator in the pivotal clinical trial in this NDA, is the standard of care in impetigo and is very effective, with cure rates of 85% and above. Many systemic antibiotics (cephalosporins as an example) are approved for the treatment of impetigo, usually as part of the skin and skin structure indication.

1.3. Important Milestones in Product Development

A. ——— was submitted on April 19, 2000. The sponsor originally desired to submit an abbreviated (generic) NDA for this product, with Bactroban Ointment as the reference product. However, it was necessary to devise a formulation different from the Bactroban formulation because the Bactroban formulation remained under patent. Since the Clay-Park formulation had different lipophilic properties than the Bactroban formulation, an ANDA was not possible.

B. December 21, 2000. Submission of the final protocol for the pivotal Phase 3 study. The sponsor briefly considered ———— indication, which is ———— . However, that plan was abandoned, and the original indication for Bactroban Ointment, impetigo, was the subject of the December 21, 2000 protocol. This protocol was found acceptable in a Medical Officer's review entered into DFS on July 26, 2001.

C. September 5, 2001. Pre-NDA meeting was held. No major issues were raised, which were not resolved.

1.4. Other Relevant Information

There are three approved NDA's which contain mupirocin. All are sponsored by GlaxoSmithKline.

A. NDA 50-746, Bactroban Ointment (mupirocin ointment) 2% is approved for the same indication that is proposed for this NDA.

B. NDA 50-746, Bactroban Cream (mupirocin calcium cream) 2% is approved for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*.

C. NDA 50-703, Bactroban Nasal Ointment (mupirocin calcium ointment) 2% is approved 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.

1.5. Important Issues with Pharmacologically Related Agents

None.

2. Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology.

A. Animal pharm/tox issues were described in Section 2.3 of the Executive Summary, above. Please see also the pharmacology/toxicology review by Dr. Amy Ellis, which states that the reviewer has no objection to approval of the NDA (entered DFS 4/22/02).

B. The Microbiology review was not available when this review was written. The following is the proposed "Microbiology" subsection of the Clay-Park package insert.

The sponsor has provided a list of references concerning various aspects of mupirocin use and safety. Many of these are general references concerning the utility of mupirocin vs. impetigo, and will not be discussed here. There are two references concerning controlled studies of mupirocin vs. oral erythromycin which will be briefly described below.

A. Dagan and Bar-David. Double-Blind Study Comparing Erythromycin and Mupirocin for Treatment of Impetigo in Children: Implications of a High Prevalence of Erythromycin – Resistant *Staphylococcus aureus* Strains. Antimicrobial Agents and Chemotherapy, 36, No. 2, 287-290, 1992.

   This was a study in 102 children under 16 years of age (median = 49 months), 93% of whom had an impetigo culture positive for *S. aureus*. The erythromycin test group received a placebo ointment (the study was fully blinded) and oral erythromycin ethylsuccinate at a dose of 50 mg/kg body weight per day. The mupirocin test group received a placebo oral formulation as well as application of 2% Bactroban Ointment 3 times daily to affected skin areas. Treatment continued for 7 days.

   In 27 of 91 (28%) of patients with *S. aureus* isolates, the organism was resistant to erythromycin. All organisms were susceptible to mupirocin. Eighty-nine patients were available for exams at the end of the study. 95% of the Bactroban patients were evaluated as cured vs 73% of the erythromycin patients. Eight of 17 (43%) of the patients with erythromycin – resistant *S. aureus* failed in the erythromycin group.

B. Goldfarb et. al. Randomized Clinical Trial of Topical Mupirocin vs. Oral Erythromycin for Impetigo. Antimicrobial Agents and Chemotherapy, 32, No. 12, 1780-1783, 1988.

   This was an open study in 62 children aged 5 months – 13 years with impetigo. The children received either Bactroban Ointment 2% on affected skin areas 3 times daily for 8 days, or erythromycin ethylsuccinate at a dose of 40 mg/kg body weight per day. Forty-nine of the patients had *S. aureus* infections, 2 had *S. pyogenes* infections, 9 had both of these organisms and the others had none or unidentified gram-negative infections. At the end of the study (7 days after drug therapy was stopped), all of the Bactroban patients were cured vs. 27 of 29 erythromycin patients. One patient in the erythromycin group had resistant *S. aureus*, and that patient failed.

As noted in the "Microbiology" subsection of the package insert, resistance has been reported to mupirocin. For the treatment of impetigo, however, an overwhelming amount of the drug is delivered directly to the disease site (resistance is seen in the range of 1000 mcg/mL while the product contains 20 mg/g mupirocin). Confirmed failure of mupirocin due to resistance in patients with impetigo has not been reported in the literature.

5. Clinical Review Methods

5.1. Describe How Review was Conducted

The summaries (safety, efficacy) provided by the sponsor were reviewed to provide a sense of the materials submitted. The database was evaluated (see section 5.3 below). The review was then written, based on the confidence of the reviewers in the submitted database.

5.2. Overview of Materials Consulted in Review

A. The NDA itself.
B. The Clinical Review Template.
C. Activity (reviews, memos) generated as a result of submission of the IND for the product.
D. Files concerning the Bactroban products (Cream, Ointment and Nasal Ointment).
E. Standard dermatological references (e.g., Dermatology in General Medicine by Fitzpatrick and others).

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

A random 15% sample of the patients in the pivotal study was generated by the FDA statistician. The sponsor was asked to submit the Case Report Forms for this random sample, and the CRFs were compared to the relevant line listings for accuracy. Previous experience has established that if the error rate in transcription of data to line listings and evaluation of results by the sponsor (cure vs. fail, adherence to inclusion/exclusion criteria, etc.) is 10% or less, the database may be relied upon in completing the review. The results of the safety studies were accepted as presented.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor has provided a statement that the trials were performed in compliance with Good Clinical Practices.

5.5. Evaluation of Financial Disclosure

The sponsor has submitted Financial Interest forms (FDA 3454) which state that none of the investigators in any of the studies (pivotal clinical, or safety) have financial interests in the outcome of the study.

6. Integrated Review of Efficacy

6.1. Brief Statement of Conclusions

The pivotal study submitted in support of this NDA establishes that Mupirocin Ointment 2% is as effective as the reference product, Bactroban Ointment, 2%. It was previously agreed by the Division that only one pivotal study was necessary, since the active ingredient has already been approved for the requested indication, and there are no other issues which would indicate that a supportive study is necessary. Please see section 2.2 of the Executive Summary for further details.

6.2. General Approach to Review of the Efficacy of the Drug

The principal parameter to be determined during the course of the efficacy review concerned whether Mupirocin Ointment performed as well as the reference product, Bactroban Ointment, in the treatment of common impetigo. The database was examined to determine whether the protocol efficacy endpoints revealed any significant difference in the effectiveness of the two test products.

6.3. Detailed Review of Trials by Indication

There was only one pivotal efficacy trial submitted in support of this application. This condition had previously been agreed to by the applicant and the Division, since the active ingredient has already been approved for the chosen indication at the same strength as is proposed in this application.

Study Title: A Multi-Center, Double–Blind, Parallel-Group Study Comparing Clay-Park Labs, Inc's. Mupirocin Ointment 2% and Bactroban® Ointment (Mupirocin Ointment, 2%) in the Treatment of Impetigo (Study No. CPL-002).

Study Dates: April 3 – September 5, 2001

Study Objectives: The following is taken directly from volume 12, p.6 of the NDA.

> Objective: The objective of the study was to demonstrate the safety and efficacy of Clay-Park Labs, Inc.'s Mupirocin Ointment, 2% (Test Product) in the treatment of impetigo compared to that of Bactroban® Ointment (Mupirocin Ointment, 2%) (SmithKline Beecham Pharmaceuticals; Reference Product).

Method:

1. Study design: This was a multicenter, randomized, parallel-group, double-blind comparison of the safety and effectiveness of Mupirocin Ointment, 2% and Bactroban Ointment, 2% in the treatment of impetigo. A total of 602 patients were randomized to receive study medication (300 Mupirocin Ointment, 302 Bactroban Ointment).

2. Inclusion criteria: The following is taken directly from volume 12, p. 25 of the NDA:

1. Subjects with a clinical diagnosis of impetigo contagiosa or uncomplicated blistering impetigo.
2. Subjects 2 months of age or older (South African subjects) or 18 months of age or older (Puerto Rican subjects) and in general good health with no known medical conditions that, in the investigator's opinion, could interfere with study participation.
3. Subjects with a SIRS score of at least 8, with at least three of the primary signs/symptoms present.
4. Female subjects of childbearing potential who had a negative urine pregnancy test result upon entry into the study and agreed to use a medically accepted form of birth control. Acceptable methods included abstinence, oral contraceptive or double-barrier method (condom or IUD with spermicide).
5. Subjects or their caregivers, in the case of children, willing and able to comply with all requirements of the protocol.
6. Subjects who provided informed consent. Subjects under 18 years of age must have had written informed consent from a parent or legal guardian. South African subjects 12 to 17 years of age and Puerto Rican subjects 7 to 17 years of age had to complete an assent form for minors.

Reviewer's Comment: The SIRS score noted in number 3 above will be described below.

3. Exclusion criteria: The following is taken directly from vol. 12 pp. 25-26 of the NDA:

1. Subjects with staphylococcal and/or streptococcal ecthyma, cellulitis, furunculosis, abscess, acute dermatitis, contact dermatitis, impetiginized eczema, or impetigo secondary to any human or animal bite, or other skin disease and/or condition located on or in close proximity to the test sites which, in the study physician's opinion, would confound the evaluation of the impetigo condition.
2. Patients whose disease is so widespread that, in the opinion of the Investigator, oral treatment is needed.
3. Patients with cutaneous herpes simplex infection.
4. Patients who have demonstrated a previous hypersensitivity reaction to mupirocin or any component of the drug.
5. Patients who have systemic signs and symptoms of a concurrent infection requiring additional antibiotic treatment.
6. Patients who have received oral antibiotic or corticosteroid treatment within 1 week prior to study start.
7. Patients with primary or secondary immunodeficiency.
8. Patients who have applied a topical steroid, antifungal, or antibacterial agent within 24 hours prior to entering the study.
9. Patients previously enrolled in this study.
10. Patients who have participated in another clinical trial or have taken an experimental drug within the past 30 days.
11. Patients who are pregnant, breast feeding or planning a pregnancy.
12. Patients with clinically significant unstable medical disorders, life threatening disease, or current malignancies.
13. Patients who are unwilling or unable to comply with the requirements of the protocol.

4. Dosage and duration of therapy: Patients were treated on the skin areas affected by impetigo 3 times daily for 7 days with one of the two test medications. The first dose was applied in the presence of the study investigator or his/her designee. Subsequent applications were made by the patient or guardian (this was an outpatient study). Washing of the infected area, including soaking of the lesions to encourage crust removal, was permitted as needed. Patient evaluations were made at

baseline, at day 3-5 of therapy, at end of therapy (day 7-9 of the study) and at follow-up a week after therapy ended (day 12-16). No topical drugs or other topical products were permitted on or near the affected areas during the study period.

5. Effectiveness parameters:

a. SIRS (Skin Infection Rating Scale)

A target lesion was identified at the baseline visit for observation in determining SIRS scores. The SIRS evaluation was made at baseline and all following visits, using the following scales. The overall SIRS score at baseline must have been at least 8 for study entrance.

BLISTERING	
0=Absent	No evidence of blisters
2=Mild	Few raised vesicles present on close evaluation
4=Moderate	Fluid filled vesicles are obvious and are bothersome to the patient
6=Severe	Extensive area covered with many vesicles which may include large bullous vesicles
EXUDATE/PUS	
0=Absent	No evidence of exudate or pus
2=Mild	Small amounts of fluid/pus coming from the lesions
4=Moderate	Exudate/pus infected area is moderate
6=Severe	Extensive areas infected and there is draining exudate
CRUSTING	
0=Absent	No evidence of crusting
2=Mild	A few areas have some evidence of crusting lesions
4=Moderate	Crusting is present throughout the infected area
6=Severe	Thick crusting appears over the entire impetiginous area
ERYTHEMA/INFLAMMATION	
0=Absent	Skin tone and color are normal; no signs of erythenma or inflammation
2=Mild	Skin is pink with minimal signs of inflammation
4=Moderate	Skin is red with definite signs of inflammation
6=Severe	Skin is red and severe inflammation is present
ITCHING/PAIN	
0=Absent	No signs of itching or indication of pain
2= Mild	Some evidence of scratching or rubbing the area is evident and patient reports minor discomfort
4=Moderate	Evidence of scratching and patient reports bothersome, painful lesions
6=Severe	Evidence of extensive scratching and patient reports pain that interferes with daily activities or sleep.

Scores of 1, 3, and 5 were used as intermediate grades for the above signs/symptoms.

b. Clinical response

Clinical response was determined by comparing the current condition of the patient to the pre-treatment condition. The primary efficacy endpoint was the clinical response at the follow-up visit. Clinical response was also determined at the end of treatment. The following scale was used:

> **Clinical success**: Sufficient resolution of signs and symptoms of infection such that no additional antibiotic therapy is required to treat impetigo as evidenced by a Skin Infection Rating Scale (SIRS) score of ≤ 1 each for blistering, exudate/pus and crusting and a SIRS score of ≤ 2 each for erythema/inflammation and itching/pain.
>
> **Clinical failure**: Additional antibiotic therapy is required to treat impetigo, as evidenced by a SIRS score > 1 for blistering, exudate/pus or crusting and/or SIRS score of > 2 for erythema/inflammation or itching/pain.
>
> **Unevaluable**: Valid clinical assessment could not be made.

c. Bacteriological response

Swabs for culture were taken at the baseline visit. Subsequent microbiological evaluations were made at end of therapy and at the follow-up visit using the following scales:

Bacteriological Success: *Staphylococcus aureus* and *Streptococcus pyogenes* are eliminated at final culture or response was such that no culture material was available and therefore evidence of pathogen eradication.

Bacteriological Failure: Non-eradication of *Staphylococcus aureus* and *Streptococcus pyogenes*.

Unevaluable: Bacteriological evaluation could not be made.

Bacterial species isolated during or after therapy that do not represent the persistence of the original pathogen will be classified as:

Microbiological Colonization: Non - pathogenic isolates from a clinical active site.

Superinfection and/or Reinfection: Clinical site has all pathogenic bacteria eradicated and on a subsequent visit clinical signs and symptoms are more pronounced and one or more pathogens are isolated.

Unevaluable: No pathogen was present from the initial culture or patient treated with antibiotics other than study drug.

6. Safety evaluation: The incidence of adverse experiences was compared

between the treatment groups.

7. Data Analyses: The data were analyzed using 3 different patient populations:

   i. All randomized (same as ITT). Analyzed for safety only. This included any patient who received at least one application of study drug.

   ii. Modified ITT. Analyzed for efficacy. This included any patient who received at least one application of study drug, had at least one post-baseline visit, and had a positive baseline microbial culture.

   iii. Per protocol. Analyzed for efficacy. This included all patients who met the inclusion/exclusion criteria, had a positive baseline culture, completed the 7 – day treatment phase, had no significant protocol violations, had a treatment compliance rate of between 66 – 133% and returned for all required visits and within the visit window for the end of treatment visit. The per protocol population is the same as the microbiologically evaluable population.

Reviewer's Comment: This protocol is adequate to determine the comparative effectiveness of the test medications in the treatment of impetigo. However, some comments are necessary:

1. **It would have been useful to perform an efficacy analysis on the (unmodified) ITT population. There were 21 patients excluded from the Mupirocin Ointment ITT group and 23 from the Bactroban Ointment group. Most of these exclusions (16 in each group) were due to a negative baseline microbial culture. It is the opinion of the reviewers that an unmodified ITT analysis is not necessary under these circumstances, providing that the modified ITT and per protocol analyses are coherent with each other.**

2. **There were some revisions to the protocol that were made after the submission of the phase 3 protocol to the IND. These were:**
   a. **Addition of the requirement that the Puerto Rican Patients be at least 18 months of age.**
   b. **Requirement that the patients may not have received more than 133% of scheduled doses to be eligible for the per protocol analysis. The previous requirement only stated that patients must have received at least 66% of scheduled doses.**
   c. **Revisions in the definition of Clinical Success. Formerly, a patient was eligible to be declared a success if the SIRS score for each sign/symptom was 2 or less. The final protocol revised this to less than or equal to 1 for blistering, exudate/pus and crusting and less than or equal to 2 for erythema/inflammation and itching/pain.**

   These revisions are acceptable.

Results:
The applicant's database was reviewed using a 15% random sample cohort. Variables analyzed included evaluability, outcome assignments and accuracy of the transposition to line listings. This review revealed disagreement between the sponsor and reviewers in 9/90 (10%) cases. The disagreements were:

1. Absence of any information in the line listings concerning the patient (except the patient number). The Case Report Form for this patient did not include any obvious errors.
2. Use of a prohibited topical medication within 24 hours of study entrance (four cases).
3. Visit window violation.
4. Failure who was not carried forward (classified as unevaluable) (two cases).
5. One patient's data listings were satisfactory, but his date of birth is given as after the study concluded.

Since the error rate was 10%, it was not necessary to produce a separate database using the assessments of the clinical reviewers. Sensitivity analyses performed by FDA statisticians indicate that the conclusions reached for the study are not altered by the results of any single investigator (see below).

The results will be presented for the modified ITT and per protocol patient populations. The data are the same as those presented by the sponsor.

1. Disposition of subjects: The following table summarizes the numbers of patients analyzed in the designated cohorts.

Table 1. Number of Patients Evaluable in Designated Cohorts

Sample	Mupirocin Ointment n (%)	Bactroban Ointment n (%)	Total n (%)
ITT (All Randomized)	300 (100)	302 (100)	602 (100)
Modified ITT	279 (93)	279 (92)	558 (93)
Per Protocol	233 (78)	242 (80)	475 (70)

It is noted that the ITT, all randomized and safety evaluable patient populations are identical. Also, the per protocol and microbiologically and clinically evaluable populations are identical. The following table gives the reasons for exclusions from the datasets by treatment group.

Table 2. Numbers of Patients Randomized and Reasons for Exclusions

	Mupirocin Ointment n (%)	Bactroban Ointment n(%)	Total n(%)
All randomized (ITT)	300 (100)	302 (100)	602 (100)
Excluded from mITT	21 (7)	23 (7.6)	44 (7.3)
Primary reason			
No post-baseline Visit	5 (1.6)	7 (2.3)	12 (2.0)
Negative culture	16 (5.3)	16 (5.3)	32 (5.3)
Excluded from per protocol	67 (22)	60 (20)	127 (21)
Primary reason			
Disc due to AE	4 (1.3)	2 (0.7)	6 (1.0)
Missed visit and visit outside of window	28 (9.3)	16 (5.3)	44 (7.3)
Lost to follow-up	9 (3.0)	17 (5.6)	26 (4.3)
Protocol violation	6 (2.0)	5 (1.6)	11 (1.8)
Negative culture[1]	17 (5.7)	16 (5.3)	33 (5.5)
Non compliance	2 (0.7)	3 (1.0)	5 (0.8)
Other[2]	1 (0.3)	1 (0.3)	2 (0.3)

[1]For one patient, a culture originally reported as negative was later reported as positive.
[2]The patient classified as "other" for Mupirocin Ointment was one of the patients checked in the validation of the database. At the end of the first week of therapy, the evaluator changed the diagnosis from impetigo to impetiginized dermatitis and exited the patient from the study. The "other" patient for Bactroban Ointment withdrew consent after the baseline visit.

The discontinuances due to adverse experiences will be discussed in the safety section below.

2. Investigators: This was a multi-center study conducted at 15 independent sites under a common protocol. Fourteen of the study sites were in South Africa, and the fifteenth was in Puerto Rico. The following presentation lists the clinical investigators and the intent-to-treat patient enrollment by investigator (the number of ITT patients is the same as the number of patients randomized). Safety analyses were performed on the entire ITT population. The presentation also includes the number of patients who were evaluable per protocol, and the number in the evaluable in the modified ITT population, defined as any patient who had at least one application of study medication, at least one post-baseline visit, and had a positive baseline culture. It should be noted that the per protocol patients are the same as the bacteriologically

evaluable patients (all clinically evaluable patients were also bacteriologically evaluable).

The percentages in the following table represent the following:

- the percentage figure following the ITT number is the proportion of the total ITT population enrolled by that investigator;
- the percentages following the per protocol and modified ITT numbers are the proportions of patients evaluable for that cohort by center, based on the ITT population for that center.

Table 3. Subject Accountability by Investigator

Study Center/ Investigator/ Location	ITT Analysis (n) (% of total ITT population)	Per Protocol Analysis (n) (% of center population)	Modified ITT Analysis (n) (% of center population)
1. J. Duursema Johannesburg, South Africa (S.A.)	7 (1)	4 (57)	6 (86)
2. A. Jacavides Midland Medical Center Johannesburg, S.A.	2 (<1)	1 (50)	2 (100)
3. U. Govind Randles Road Medical Center, Durban, S.A.	5 (1)	4 (80)	5 (100)
4. S. J. Glassman Wits Medical School Johannesburg, S.A.	12 (2)	11 (92)	12 (100)
5. M. J. Heystak Mamelodi Hospital Pretoria, S.A.	8 (1)	8 (100)	8 (100)
6. S. J. Schmidt Cape Town, S.A.	148 (24.6)	128 (86.5)	139 (93.9)
7. N. Raboobee Westville Hospital Durban, S.A.	9 (1.5)	7 (78)	7 (78)
8. J. Aboobaker University of Natel Durban, S.A.	20 (3)	4 (20)	18 (90)

9. G. Todd University of Cape Town Cape Town, S.A.	136 (22.6)	103 (75.7)	129 (94.9)
10. M. S. Ismail Prime Cure Clinic Cape Town, S.A.	19 (3)	10 (53)	17 (89)
11. A. L. Barrett Prime Cure Clinic Pretoria, S.A.	12 (2)	12 (100)	12 (100)
12. D. J. J. van Rensburg Park Medical Center Wilbank, S.A.	14 (2)	9 (64)	10 (71)
13. H. Davis South Africa Clinical Trials George, S.A.	124 (20.6)	104 (83.9)	116 (93.5)
14. W. H. Eaglstein U. of Miami School of Medicine Miami, FL	86 (14.3)	70 (81.3)	77 (89.5)
TOTAL	602	475	558

Reviewer's Comment: The investigator at one center (S. Furman) did not enroll any patients and is not included in the above table. It is noted that while Dr. Eaglstein's mailing address is in Miami, his portion of the study took place in Santurce, Puerto Rico. His co-investigator there was [redacted]

In addition, it can be seen that four of the 15 investigators (Drs. Schmidt, Todd, Davis and Eaglstein) enrolled about 82% of the total number of patients. Of the 602 patients in the ITT sample, 475/602 (79%) were analyzable per protocol and 558/602 (92.7%) were analyzable in the modified ITT group by the sponsor's standards.

3. Demographics: The following table, which is adapted from Table 4 on p.45 of volume 1.12 of the NDA, provides the demographic characteristics for the ITT population. The demographics for the mITT and per protocol population were very similar to these.

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Table 4.
Demographic Characteristics for Intent-to-Treat Subjects

Parameter	Mupirocin Ointment, (N=300)	Bactroban® Ointment (N=302)	p-value
Gender (n,%)			
Male	146 (49%)	144 (48%)	0.793
Female	154 (51%)	158 (52%)	
Race (n,%)			
White	12 (4%)	10 (3%)	0.683
Black	174 (58%)	182 (60%)	
Other	114 (38%)	110 (36%)	
Age (years)			
Mean ± Std	9.18 ± 10.06	8.75 ± 9.20	0.926
Min – Max	0.2 - 58.6	0.3 - 54.0	
Number (%)of Subjects			
<=5	132 (44%)	131 (43%)	
6-10	88 (29%)	94 (31%)	
11-15	36 (12%)	39 (13%)	
>15	44 (15%)	38 (13%)	

Reviewer's Comment: The "Other" category in the above table was defined by the applicant as "South African colored or mulatto".

4. Effectiveness Parameters

A. The primary efficacy parameter was clinical response at followup. The results are presented in the following table, which is similar to Table 6 on p. 51 of volume 12 of the NDA. As noted previously, results will be presented for the per protocol and modified ITT populations.

Table 5. Clinical Response at Follow-up

	Mupirocin Ointment	Bactroban® Ointment	Two-Sided 95% C.I.
Clinical Response: Per-Protocol Subjects (n,%)			
	(N=233)	(N=242)	
Success	218 (94%)	231 (95%)	-6.41% to 2.63%[1]
Failure	15 (6%)	11 (5%)	
Clinical Response: Modified Intent-to-Treat Subjects (n, %) – Planned Analysis[2]			
	(N=279)	(N=279)	
Success	249 (89%)	251 (90%)	-6.14% to 4.71%[1]
Failure	30 (11%)	28 (10%)	

Clinical Response: Modified Intent-to-Treat Subjects (n, %) – SensitivityAnalysis[3]

	(N=279)	(N=279)	
Success	254 (91%)	255 (91%)	-5.41% to 4.70%[1]
Failure	25 (9%)	24 (9%)	

[1]Confidence intervals calculated using Wald's method with Yate's continuity correction.
[2]A response of 'Unevaluable' was treated as a missing efficacy result, and missing efficacy results were treated as failures in the analyses.
[3] A response of 'Unevaluable' was treated as a missing efficacy result, and a last observation carried-forward approach was used for missing efficacy results.

Because four investigators provided most of the patients, it is felt that presentation of their individual results would be useful.

Table 6. Clinical Success at Followup (High Enrollers)

Clinical Success:	Mupirocin Ointment Subjects, N (%)	Bactroban Ointment Subjects, n (%)	95% C.I.
Per Protocol			
Schmidt	62/62 (100)	65/66 (98)	(-3.0, 6.0)
Todd	42/50 (84)	51/53 (96)	(-25.6, 1.1)
Davis	49/51 (96)	48/53 (91)	(-5.9, 16.9)
Eaglstein	33/36 (92)	32/34 (94)	(-17.3, 12.4)
Modified ITT			
Schmidt	67/69 (97)	69/70 (99)	(-7.7, 4.8)
Todd	54/65 (83)	58/64 (91)	(-20.7, 5.6)
Davis	51/59 (86)	48/57 (84)	(-12.4, 16.8)
Eaglstein	38/33 (87)	32/39 (82)	(-13.9, 23.5)

Reviewer's Comment: The combined data establish that Mupirocin Ointment, 2% performed as well in the principal efficacy endpoint as Bactroban Ointment did. Dr. Todd found Bactroban to be slightly more effective than Mupirocin Ointment. The homogeneity of treatment effect was evaluated by the FDA statistician. Using Breslow-Day's test, he found a p-value for the per protocol patient population of 0.098, and for the modified ITT population, 0.524.

Since nearly all patients were cured, subgroup efficacy analysis is not useful. However, it may be instructive to briefly list the characteristics of the failures in each treatment group, since there were so few of them.

Table 7. Per Protocol Failures

Treatment	Patient No.	Investigator	Age(yrs.)	Sex	Pathogen
Mupirocin	44	Raboobee	12	M	*Strep*
Ointment	45	Raboobee	12	M	*Strep, Staph*
(n=15)	227	Todd	13	M	*Strep, Staph*
	228	Todd	2.6	M	*Strep, Staph*
	230	Todd	4.7	M	*Strep, Staph*
	307	Todd	2.8	M	*Strep, Staph*
	394	Davis	15	F	*Strep*
	454	Todd	8	F	*Strep, Staph*
	455	Todd	4.3	F	*Strep*
	459	Todd	3.6	M	*Strep, Staph*
	505	Davis	9	M	*Strep*
	525	Todd	0.2	M	*Strep, Staph*
	590	Eaglstein	3.8	F	*Staph*
	602	Eaglstein	1.9	M	*Staph*
	614	Eaglstein	28	F	*Staph*
Bactroban	23	Schmidt	1.6	M	*Strep, Staph*
Ointment	55	Davis	0.6	F	*Strep, Staph*
(n=11)	93	Davis	6	F	*Strep, Staph*
	105	Davis	12	M	*Strep, Staph*
	143	Duursema	20	F	*Strep, Staph*
	255	Todd	7	M	*Strep, Staph*
	259	Todd	6	M	*Strep, Staph*
	338	Davis	9	M	*Strep, Staph*
	373	Todd	3.0	F	*Strep, Staph*
	508	Davis	10	F	*Strep, Staph*
	595	Eaglstein	2.2	F	*Strep, Staph*

Reviewer's Comment: These results are unremarkable, though Dr. Todd had a higher percentage of failures (especially for Mupirocin Ointment) than did the other investigators. In addition, Dr. Eaglstein's patients predominantly were infected with *S. aureus* only. This does not seem to have affected his results.

B. Secondary effectiveness parameters

i. Clinical response at end of therapy

The following table presents the results for clinical response for the pooled investigators at the end of therapy. It is adapted from table 7 on p. 53 of volume 12 of the NDA.

iii. SIRS scores

The following table presents the total sign and symptom (blistering, exudate/pus, crusting, erythema/inflammation and itching/pain) scores at baseline, end of therapy and test of cure for the per protocol patients.

Table 10. Mean SIRS Scores for Per Protocol Patients

Visit	Mupirocin Ointment	Bactroban Ointment	p-value[1]
Baseline			
N	233	242	
Mean	16.98	17.19	0.389
SD	4.83	4.57	
End of therapy			
N	233	242	
Mean	1.38	1.40	0.810
SD	2.00	1.99	
Followup			
N	233	242	
Mean	0.47	0.38	0.957
SD	1.52	0.83	

The following table presents the same information for the mITT patients.

Table 11. Mean SIRS Scores for mITT Patients

Visit	Mupirocin Ointment	Bactroban Ointment	p-value[1]
Baseline			
N	279	279	
Mean	17.08	17.22	0.552
SD	4.70	4.53	
End of Therapy			
N	279	279	
Mean	1.63	1.59	0.737
SD	2.57	2.20	
Followup			
N	279	279	
Mean	0.73	0.67	0.847
SD	2.03	1.48	

1= P-values for treatment comparisons from Friedman's test. Missing scores were not included in the calculations of p-values or descriptive statistics.

C. Pathogen eradication rates
The following table lists the eradication rates for the two applicable pathogens in the microbiologically evaluable subjects.

Table 12. Pathogen Eradication Rates at Test of Cure

Pathogen	Mupirocin Ointment	Bactroban Ointment
Strep. pyogenes	180/185 (97%)	180/184 (98%)
Staph. aureus	187/191 (98%)	188/192 (98%)

Note: Each entry above includes four patients who were discontinued due to treatment failure and were carried forward as microbiological failure.

The majority of patients in the study had mixed (both *Strep* and *Staph* infections). However, there were significant numbers of individuals with infections related to only one pathogen. In the mITT population, there were 54 patients in both the Mupirocin Ointment and Bactroban Ointment cohorts who had only *Strep*, while there were 58 patients in the Mupirocin cohort and 68 in the Bactroban cohort who had only *Staph*.

Reviewer's Comment: The literature examined by the reviewers does not suggest that mixed infections are more difficult to cure than infections caused by single pathogens. If one refers to Table 7 in section 3.A. above, which describes per protocol failures, it can be seen that 20 of 26 failures involved mixed infections. These numbers are too small to support reliable conclusions.

6.4 Efficacy Conclusions
This study establishes that Mupirocin Ointment, 2% is as effective as Bactroban Ointment in treating impetigo caused by *Staphyloccus aureus* and/or *Streptococcus pyogenes* in adults and children down to the age of 2 months. There were three children 2 months of age in the Mupirocin Ointment group, which is the same number of children of that age in the Bactroban Ointment pivotal studies. Therefore, it is acceptable to grant the same lower age limit for Mupirocin Ointment.

Cure rates in the per protocol population were 94% for Mupirocin Ointment and 95% for Bactroban Ointment at the followup visit, while bacteriological response for the same population and time frame was 98% for both groups. The appropriate patient populace was studied, and the protocol was well designed.

7. Integrated Review of Safety

7.1. Brief Statement of Findings

Mupirocin Ointment is safe for the treatment of impetigo at the stated dosage. There were relatively few adverse events (7/300=2.3%) attributed to Mupirocin Ointment use by the investigators, and these were not serious. No deaths were seen during the pivotal study. Three serious adverse events (bronchospasm, accidental ingestion of paraffin and acute glomerulonephritis with hypertension secondary to a strep infection) were reported that the investigators considered not related to drug therapy.

The predictive skin toxicity studies did not produce results indicative of potential for irritation or sensitization. The absorption study indicated that about four times more Mupirocin Ointment than Bactroban Ointment was absorbed through normal adult skin. However, this is a very small amount compared to systemic amounts which have been successfully tested for toxicity.

7.2 Materials Utilized in the Review

The NDA safety database was utilized in the review of safety.

7.3 Description of Patient Exposure

Please see section 2.3 of the Executive Summary for details of patient exposure.

7.4 Safety Findings from Clinical Studies

A. Adverse events in the pivotal clinical study

The following table, which is similar to Table 11 on p.61 of volume 12 of the NDA, summarizes those adverse events which were considered skin related.

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Table 13. Summary of skin related events

	Number (%) of Subjects	
	Mupirocin Ointment (N=300)	Bactroban Ointment (N=302)
Total skin related events	12 (4.0%)	13 (4.3%)
Application site reaction	3 (1.0%)	3 (1.0%)
Contact dermatitis	2 (0.7%)	6 (2.0%)
Eczema	0	1 (0.3%)
Exfoliative dermatitis	1 (0.3%)	0
Furunculosis	2 (0.7%)	0
Maculopapular rash	0	2 (0.7%)
Pruritus	3 (1.0%)	2 (0.7%)
Rash	1 (0.3%)	0
Vesiculobullous rash	0	1 (0.3%)

Note: There were 15 events in 13 patients in the Bactroban group

The following table, which is similar to Table 3.17 in the Integrated Statistical Report in volume 18 of the NDA, provides the investigator's assessment of severity and relationship to drug for the skin related events.

Table 14
Adverse Events by Severity and Relationship for Skin-Related Events

	Number (%) of Subjects		
Parameter	Mupirocin Ointment (N=300)	Bactroban® Ointment (N=302)	p-value Mupirocin Versus Bactroban
Number (%) of Adverse Event(s) Reported	12	13	
Severity of Event			
Mild	8 (67%)	11 (85%)	0.655[1]
Moderate	4 (33%)	1 (8%)	
Severe	0	1 (8%)	
Relationship of Event to Study Drug			
Unknown	1 (8%)	1 (8%)	0.722[1]
Unrelated	4 (33%)	8 (62%)	
Probably Related	3 (25%)	1 (8%)	
Related	4 (33%)	3 (23%)	

[1]P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site.

The following table, which is the same as Table 3.19 in the Integrated Statistical Report in volume 18 of the NDA, lists the adverse events which were not skin related .

Table 15
Summary of Adverse Events by Body System for Non-Skin Related Events

	Mupirocin Ointment (N=300)	Bactroban Ointment (N=302)
Body System[1]		
Body as a whole	17 (5.7%)	9 (3.0%)
Abdominal pain	1 (0.3%)	0
Abscess	1 (0.3%)	0
Accidental injury	5 (1.7%)	4 (1.3%)
Cellulitis	1(0.3%)	0
Fever	4 (1.3%)	1 (0.3%)
Flu sydrome	2 (0.7%)	2 (0.7%)
HIV test positive	1 (0.3%)	0
Infection	1 (0.3%)	3 (1%)
Viral infection	2 (0.7%)	0
Metabolic and nutritional disorders	1 (0.3%)	0
Edema	1 (0.3%)	0
Nervous system	1 (0.3%)	0
Hostility	1 (0.3%)	0
Nervous system/cardiovascular system	1 (0.3%)	0
Hypertension	1 (0.3%)	0
Respiratory system	26 (8.7%)	17 (5.6%)
Asthma	1 (0.3%)	0
Bronchiolitis	3 (1.0%)	6 (2.0%)
Bronchitis	2 (0.7%)	0
Cough increased	4 (1.3%)	3 (1.0%)
Pharyngitis	16 (5.3%)	6 (2.0%)
Pneumonia	1 (0.3%)	0
Rhinitis	1 (0.3%)	2 (0.7%)
Special senses	3 (1.0%)	3 (1.0%)
Conjunctivitis	1 (0.3%)	0
Otitis externa	1 (0.3%)	0
Otitis media	1 (0.3%)	3 (1.0%)
Urogenital system	2 (0.7%)	0

Dysuria	1 (0.3%)	0
Glomerulitis	1 (0.3%)	0
Menstrual disorder	1 (0.3%)	0
Urinary frequency	1 (0.3%)	0

[1]Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) subjects are only counted once. Percentages of subject in each treatment group are also given.

In the opinion of the reviewers the only event in this presentation which could have possibly been related to the drug (lack of effectiveness) was the case of cellulitis in the Mupirocin Ointment group.

There were four Mupirocin Ointment patients and two Bactroban Ointment patients who discontinued due to adverse events. These were:

A. Mupirocin Ointment

i. Patient with acute bronchospasm, not related to drug therapy.
ii. Patient with upper respiratory tract infection, not related to drug therapy.
iii. Patient with glomerulonephritis, not related to drug therapy.
iv. Patient with cellulitis who was discontinued after the day 3 visit. This event was possibly related to lack of drug effectiveness.

B. Bactroban Ointment

i. Patient discontinued with papular lesions surrounding his impetigo lesions. This event was probably related to lack of drug effectiveness.
ii. Patient with otitis media, not related to drug therapy.

B. Cumulative Irritation Study

Study Title: A Randomized, Double-Blind Assessment of the Primary Irritation Potential of 2% Mupirocin Ointment and its Vehicle as well as a Reference Product (Bactroban® Cream) Using a 21-Day Cumulative Irritation Test (Study: KGL #4681).

Investigator: Kays Kaidbey, M.D.
Ivy Laboratories
Philadelphia, PA 19104

Study Dates: July 10-31, 2000.

Study Objectives: The following is taken directly from p.6 of the study report in volume 11 of the NDA:

> The objective of this randomized double-blind parallel study on healthy human volunteers was designed (sic) to comparatively evaluate the primary irritancy

potential of Mupirocin Ointment (test product) and its vehicle (Mupirocin Ointment, 2% - Placebo) to Bactroban® Cream [mupirocin calcium cream], 2% (reference product) in a 21-day cumulative irritation assay.

Method:

1. Study Design: This was a paired comparison of Mupirocin Ointment, 2%, its vehicle and Bactroban Cream in which each test subject served as his or her own control. The study also included normal saline as a negative control and 0.1% aqueous sodium lauryl sulfate as a positive control. Thirty test subjects began the study and 27 completed it. The evaluator was blinded concerning the identity of the products tested.

2. Inclusion Criteria: The following is taken directly from p. 13 of the study report in volume 11 of the NDA:

1 – All were healthy adult male and female volunteers between the ages of 18 and 60 years.
2 – All subjects were willing to follow the study requirements and voluntarily gave their signed informed consent.
3 – All subjects were in good general health.
4 – None had any diseases, skin conditions or allergies that would have interfered with the study.
5 – None were under treatment with any systematic or topical steroid or any other medication that would have interfered with the expression of cutaneous inflammation (e.g., immunosuppressants).
6 – No female was pregnant or nursing and all women of childbearing potential were practicing adequate birth control measures, as determined by the investigator (method was determined prior to starting the study).
7– All were willing to refrain from swimming and sunbathing for the duration of the study.

3. Exclusion Criteria: The following is taken directly from pp.13-14 of the study report in volume 11 of the NDA:

1 – All subjects with a significant history of past or ongoing internal disease, e.g., renal, hepatic, pulmonary, neurologic etc.
2 – Subjects with recurrent dermatological conditions, e.g. psoriasis, eczema.
3 – Scars, moles or other blemishes over the test site which would have interfered with the study.
4 – Subjects with recent sunburn or excessive sun exposure (within the previous 2 weeks).
5 – Subjects receiving systemic or topical drugs including steroidal or non-steroidal anti-inflammatory drugs, retinoids, antihistamines or medications which would have interfered with the expression of cutaneous inflammation. (Subjects had to be off oral steroids or retinoids for at least 4 months prior to enrollment).
6 – History of allergy, hypersensitivity or irritation to the study products.
7 – Pregnancy or mothers who were breastfeeding.
8 – Participation in an investigative study within the previous 4 weeks.
9 – Subjects who were known to be HIV positive.
10 – Subjects who were abusers of alcohol and other drugs.

11 – Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

3. Dosage and Duration of Therapy: Approximately 0.1 mL of each test material was applied to designated test sites measuring 15 mm in diameter on the upper arm or lower back. The test sites were then covered with occlusive dressings. The patches were left in place for 24 hours, at which time they were removed and graded for irritation. The patches were then replaced and the process repeated 5 times weekly (the patches remained in place for the weekend).

4. Scoring Scale: The responses were graded on the following scale:

Score:		Description:
0	=	no erythema (normal skin)
1	=	minimally visible (flat) erythema
2	=	moderate erythema with sharply defined borders
3	=	intense erythema with edema (elevated lesion)
4	=	intense erythema with edema and vesicles or erosion(s)

If at any time, a score of 3 or greater was seen in a test site, further applications to that site were discontinued and the highest score (3 or 4) was carried through for the remainder of the test period for the purpose of calculating the cumulative irritation score.

Results:

1. Withdrawals: Three of the 30 subjects who entered the study withdrew prior to its completion. Reasons for these withdrawals were not given. One patient did not return after the baseline examination, while the other two discontinued after one week. The test scores for the latter two subjects did not indicate irritation at the time of withdrawal.

2. Demographics: There were 12 females and 18 males in the group who entered the Study, aged 18-56 years. All the subjects were Caucasian, which is typical in studies of this type in that irritation reactions are more apparent in lighter-skinned test subjects.

3. Irritation: The simplest means of presenting the irritation scores is to sum the results for all subjects at all readings. The following table presents this summary.

Table 16 - Total Irritation Scores

Test Material	Total Group Score
Mupirocin Ointment, 2%	9

Mupirocin Vehicle	13
Bactroban Cream	8
0.1% Sodium Lauryl Sulfate	151
Normal Saline	18

4. Adverse Reactions: There were two reports of adverse events during the study, including one case of generalized muscle aches and one upset stomach. Neither event was felt to be study related.

Reviewer's Comment: This study follows a standard protocol for determination of the irritancy potential of drug products. The results indicate that Mupirocin Ointment has a very low irritancy potential. (rather than Bactroban Ointment) was used during this study because the at the time.

C. Contact Sensitization Study

Study Title: A Double-Blind Assessment of the Contact-Sensitizing Potential of 2% Mupirocin Ointment and its Vehicle as well as a Reference Product (Bactroban Cream) by means of the Jordan Modification of the Draize Test (Study: KGL #4682).

Investigator: Kays Kaidbey, M.D.
Ivy Laboratories
Philadelphia, PA 19104

Study Dates: September 25 – December 7, 2000.

Study Objectives: The following is taken directly from p. 6 of the study report in volume 11 of the NDA:

> The objective of this study was to determine the contact-sensitization (allergenic) potential of 2% Mupirocin Ointment (test product) and its Vehicle using a Jordan modification of the Draize Assay in normal healthy subjects. A comparable marketed product (Bactroban® Cream, reference product) was also evaluated simultaneously for comparison.

Method:

1. Study Design: This was a paired comparison of Mupirocin Ointment, 2%, its vehicle, and Bactroban Cream in which each test subject served as his or her own control. Petroleum jelly was also included as a negative control. Two hundred seven subjects began the study and one hundred ninety one completed it. The evaluation was blinded concerning the identity of the products tested.

2. Inclusion Criteria: These were the same as for the irritation study, above.

3. Exclusion Criteria: These were similar to those for the irritation study, with the following exceptions:

   i. The second and third exclusion criteria in the irritation study, concerning subjects with recurrent dermatological conditions and subjects with scars, moles, etc, over the test site have been omitted.
   ii. An additional exclusion criterion has been added, as follows: "history of recurrent urticaria or hives."

4. Dosage and Duration of Therapy: This test was performed in three phases, as follows:

   a. Induction phase: Approximately 0.1 mL of each test material on a cloth patch was applied to designated test sites of unspecified size on the upper arm or lower back. The test sites were then covered with occlusive dressings. The patches were left in place for 48 hours (72 hours over a weekend). This sequence was repeated over 3 weeks, for a total of 9 new patch applications. The test sites were evaluated for irritation at each patch change. If an irritation grade of 2+ or greater was seen, the patch site was moved to a nearby skin area and applications were continued.

   b. Rest period: Following the last induction application, a 10 to 14 day rest period took place during which no patches were applied.

   c. Challenge phase: After the rest period, the subjects were challenged with a 0.1 mL application of the test materials at a new, previously untested site on the opposite upper arm or lower back. The patches were left in place for 48 hours and graded for sensitization 15 minutes and 24 hours after patch removal.

5. Scoring Scales: The sensitization responses were graded on the following scale:

   0 = not sensitized

   1 = mild sensitization (viz. erythema and a little edema)

   2 = moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)

   3 = strong sensitization (large vesicula-bullous reaction)

Results:

1. Withdrawals: Sixteen of the 207 subjects who entered the study withdrew prior to its completion. Six voluntarily withdrew, eight others failed to report at some point during the induction phase, and two others failed to report for the challenge phase. No reasons for these withdrawals are given. However, the irritation scores for these patients have been examined to the point at which they left the study. No irritation was seen in any of the subjects.

2. Demographics: There were 107 males and 100 females in the group who entered the study, aged 18-60 years. Four were of Asian descent, while the rest were Caucasian.

3. Sensitization: None of the test subjects displayed any sensitization to any of the test products in the challenge phase.

4. Adverse Reactions: Three test subjects reported headaches during the course of the study, which were not judged to be study related.

Reviewer's Comment: This study followed a standard protocol to determine the sensitization potential of drug products. None of the products tested displayed any sensitization potential.

D. Human Absorption Study

Study Title: A Randomized, Crossover Study on Healthy, Normal Subjects to Compare Systemic Exposure to Mupirocin after Multiple, Once-Daily Doses of Two Mupirocin Ointment 2% Products. (Study: FARMOVS 125/2001)

Investigator: Dr. J Terblanche
FARMOVS-PAREXEL Clinical
Bloemfontein, South Africa

Study Dates: November 5 – December 10, 2001

Method: This study will not be described in detail, as a critical review is being performed by CDER biopharmaceutics personnel. This was a crossover design in which each test subject served as his or her own control. Twenty-four test subjects were initially administered 2 grams of Bactroban Ointment (containing 40 mg mupirocin) to a specified area on the body once daily, for seven days. The test area was occluded for 12 hours on each day. An 8 day washout period followed.

The final phase involved administering 2 grams of Mupirocin Ointment to the test subjects in an identical fashion to the Bactroban Ointment application.

Absorption was measured by determining each subjects cumulative urinary monic acid excretion over the 24 hours following the final dose on day 7. Monic acid is the principal metabolite of Mupirocin, which dissociates very quickly upon entering systemic circulation.

Results:

1. Withdrawals: One subject withdrew from the study because of work-related obligations after the Bactroban phase of the study.

2. Demographics: There were 14 males and 10 females enrolled in the study. All were Caucasians.

3. Absorption: The mean cumulative monic acid excretion one hour after drug administration was 7.3 micrograms for Bactroban Ointment and 14.4 micrograms for Mupirocin Ointment. After 24 hours, the mean monic acid excretion was 80.9 micrograms for Bactroban and 355.9 micrograms for Mupirocin. As a percentage of dose, the mean cumulative monic acid excretion at 24 hours was 0.29% for Bactroban Ointment and 1.29% for Mupirocin Ointment.

4. Adverse Reactions: Four of the 24 test subjects reported adverse events. Two of these were headaches, not judged to be drug related. The other two reactions were possibly drug related. The first was a rash in one subject for one day while on Mupirocin. The second was in a different subject who experienced itching during the entire seven day Bactroban application.

Reviewer's Comment: Final evaluation of this study will be performed by the biopharmaceutics reviewer. The results indicate that the Mupirocin Ointment formulation carries the active ingredient through healthy skin at about four times the level that the Bactroban Ointment formulation does. The significance of this finding is modified by the information that systemic administration of a much higher mupirocin dose (250 mg) during development of the Bactroban product did not produce any apparent effects.

The reviewers either have no information to review or have already addressed the subject for the following sections of the review template;

7.5 Miscellaneous Studies
7.6 Literature Review for Safety
7.7 Postmarketing Surveillance
7.8 Safety Update

7.9. Drug Withdrawal, Abuse, and Overdose Experience

There is no known potential for abuse of mupirocin. Overdosage has not been reported. Given the pattern of use and the toxicity profile of the drug, overdosage is not likely.

7.10. Adequacy of Safety Testing

The drug has been adequately tested for safety. Please see section 2.3 of the Executive Summary for synopses of the relevant studies.

7.11. Labeling Safety Issues and Postmarketing Commitments

The labeling for Mupirocin Ointment closely follows the approved labeling for Bactroban Ointment. There are no outstanding safety issues with the labeling, and no postmarketing commitments are necessary.

8. Dosing, Regimen, and Administration Issues

There are no changes from the dosage and administration section used for Bactroban Ointment. As noted above, impetigo is so easily treated by mupirocin that it is entirely possible [redacted] (rather than the recommended three) would be effective; however, [redacted] has not been studied for efficacy and since three applications produces low toxicity, there seems to be no reason to pursue this.

9. Use in Special Populations

9.1. Evaluation of Applicant's Efficacy and Safety

Analyses of Gender, Age, Race, or Ethnicity. Comment on Adequacy of the Applicant's Analyses.

As noted above, the lack of Caucasian patients in this study is unusual, but there is no medical or scientific information available to imply that race is a factor in impetigo. In any case, Bactroban Ointment was originally tested successfully in a predominantly Caucasian patient cohort, and its use in the non-Caucasian patients seen in this NDA was also successful. This would indicate that race is not a factor in the treatment of impetigo with mupirocin.

The sponsor has submitted analyses comparing clinical response rates in the per protocol and modified ITT patient cohorts by sex and age, for the individual treatments and for the total database (Bactroban and Mupirocin patients combined). The age analyses were segmented into the groups used in the demographic tables (less than 5 years, 6-10 years, etc). No significant differences were seen in any of the comparisons.

9.2. Pediatric Program

The patients tested in this NDA were predominantly in the pediatric age group. No additional pediatric information is needed to provide safe dosing recommendations in the pediatric population. The sponsor has requested a waiver for testing of patients younger than 2 months of age. These patients are likely to be treated with Mupirocin Ointment, even though the label does not recommend such use. The basis for the waiver request is that pediatric studies are highly impractical in this age group because the number of prospective patients is so small and geographically dispersed. The waiver request may be granted, both because the sponsor's statement is accurate, and because there is no information to indicate that Mupirocin Ointment will be any less effective or more toxic in these younger children.

9.3. Data Available or Needed in Other Populations such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

No data is needed in other populations.

10. Conclusions, Recommendations, and Labeling

10.1. Conclusions Regarding Safety and Efficacy

This application establishes that Mupirocin Ointment, 2% is highly effective in the treatment of impetigo caused by *Staphylococcus Aureus* and *Streptococcus Pyogenes*. It is expected that this product will cure 90% or more of treated patients when used three times daily for 7 days. The safety profile of the product is excellent. The formulation to be marketed does not display any potential for skin irritation or sensitization when tested by standard methods. Adverse events were observed in 4% of patients and were skin-related. This product should be safe when used as directed.

10.2. Recommendations on Approvability

This drug may be approved from a clinical perspective. No additional information is necessary to complete the application.

10.3. Labeling

The labeling for this product is based on the label for Bactroban Ointment. There are minor differences in the labeling (trade name, manufacturer, location of prescription only statement) which do not require comment. The following items describe the instances in which the Mupirocin and Bactroban labels differ significantly.

A. Description

The inactive ingredients for the two products differ.

B. Clinical Pharmacology

In the second sentence of the Microbiology subsection, the phrase [redacted] has been deleted at the request of the Division. A study which establishes the effectiveness of this formulation against MRSA is necessary to support this statement.

C. Precautions

i. In the second paragraph, the sentences " [redacted] have been replaced by "Mupirocin Ointment, 2% is not intended for nasal use."

ii. In the third paragraph, the statement concerning [redacted] has been omitted, since Mupirocin Ointment does not contain this ingredient.

D. Adverse Reactions

The adverse events for Bactroban have been deleted and replaced by the adverse events for Mupirocin. Some of the Mupirocin reactions have been omitted from this tabulation and should be added. This section should read as follows:

> The following local adverse reactions have been reported in connection with the use of Mupirocin Ointment, 2%: application site reactions and pruritus, each in 1% of patients; contact dermatitis and furunculosis, each in 0.7% of patients; and exfoliative dermatitis and rash, each in 0.3% of patients.

The statement in the Bactroban labeling concerning systemic reactions to that product has been omitted, since reactions of this type were not reported for Mupirocin Ointment.

E. Clinical Studies

The information concerning Bactroban has been deleted and replaced by information summarizing the Mupirocin studies. This information is generally satisfactory, although the following comments are necessary.

i. The following statements should be omitted from the end of the sponsor's

proposed section:

[redacted]

[redacted]

In summary, the proposed labeling is satisfactory with the exceptions in the Adverse Reactions and Clinical Studies sections noted above.

Bostwick
Mulinde
Soreth
Jiang
Lin
Sheldon

David Bostwick

Jean Mulinde, MD

APPEARS THIS WAY
ON ORIGINAL

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/s/

Janice Soreth
12/4/02 06:51:19 PM
NDA 50-788 Approval letter & labeling

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ON ORIGINAL

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/s/

David Bostwick
9/16/02 10:38:46 AM
MEDICAL OFFICER

Jean Mulinde
9/16/02 10:44:01 AM
MEDICAL OFFICER

Janice Soreth
10/24/02 02:14:37 PM
MEDICAL OFFICER

ADDENDUM TO PRIMARY CLINICAL REVIEW
NDA 50-788

Date of Original Submission: February 7, 2002

Date of Review Initiation: October 31, 2002

Drug: Mupirocin Ointment, 2%

Applicant: Clay-Park Labs, Inc.
Bronx, NY 10457

Reasons for Addendum:
A. Statement of additional revision to the package insert which was not included in the original clinical review.
B. Completion of the Pediatric Page for the NDA.

Review:
A. Labeling revision
There is an inaccuracy in the proposed CLINICAL STUDIES section of the package insert for this product. The section states efficacy rates at the followup visit but erroneously connects them to the end of therapy visit. In order to correct this error and provide consistency in statements of the clinical and microbiological cures, the third and fourth sentences in the CLINICAL STUDIES section should read as follow:

> Clinical efficacy rates at the followup visit (one week after end of therapy) in the evaluable populations (adults and pediatric patients included) were 94% for Mupirocin Ointment, 2% (N=218) and 95% for Bactroban Ointment (Mupirocin Ointment 2%) (N=231). The pathogen eradication rates at followup for both medications were 98%.

B. Pediatric Page
The Pediatric Page for this application is attached.

David C. Bostwick

Jean Mulinde, MD

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/s/

David Bostwick
11/4/02 10:50:18 AM
MEDICAL OFFICER

Jean Mulinde
11/4/02 10:52:03 AM
MEDICAL OFFICER

Janice Soreth
11/7/02 01:21:26 PM
MEDICAL OFFICER

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☒ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** >2	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
David C. Bostwick_____