Approval Date: September 28, 1988

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-839

B. Sponsor

Beecham Laboratories
501 Fifth St.
Bristol, TN 37620

C. Proprietary Name

BACTODERM®

D. Established Name

mupirocin

E. Dosage Regimen

Prior to treatment the lesion should be cleansed.

BACTODERM Ointment should be applied to the affected area twice a day. Apply a sufficient amount of ointment to completely cover the affected area. The maximum duration of treatment should not exceed 30 days.

F. Indication

BACTODERM® Ointment is indicated for the topical treatment of canine bacterial infections of the skin, including superficial pyoderma, caused by susceptible strains of the following organisms: *Staphylococcus aureus* and *Staphylococcus intermedius*.

II. EFFECTIVENESS

The effectiveness of BACTODERM for canine bacterial skin infections was demonstrated in experimentally induced infection models and a well-controlled field study.

A. Pivotal Studies

1. Experimentally Induced *S. intermedius* Infection Study

An experimentally induced *Staphylococcus intermedius* skin abrasion study was conducted in dogs by Dr. R. Garg, Tuskegee University, Tuskegee, Alabama. The study was conducted as a double-blind, randomized, parallel group design.

A total of 23 dogs were used in this study. Nine dogs were treated with BACTODERM Ointment, nine with the vehicle ointment and five were non-treated controls. The study model consisted of clipping the hair along the

dorsal midline and then shaving a two inch by two inch area. This area was surgically scrubbed and then abraded. This abraded area was inoculated both topically and intradermally with 2 ml of a 24-hour broth containing *Staphylococcus intermedius*. Eight hours later, the sites were reinoculated topically.

Treatment was initiated 48 hours after the initial inoculation and was continued twice a day for five days. A thin layer of medication was spread over the lesion.

Bacteriological evaluation, the pivotal parameter, was performed on days 2, 4, 6, 7, 9, and 11. Clinical observations were made on days 1-7, 9 and 11. Two investigators independently evaluated the lesions for swelling, pain, exudation, erythema and pruritus.

Bacteriological results were based upon complete elimination of *S. intermedius* from lesions. The antimicrobial effect of mupirocin was evident as early as 48 hours after initiation of treatment. By the last day of treatment, 78% of the animals in the BACTODERM group were negative for the challenge pathogen compared to 33% for the vehicle. At 72 hours and 120 hours post-treatment, 100% of the animals treated with mupirocin were negative compared to 89% and 78% for the vehicle. At no time during the study was *S. intermedius* eliminated from the no-treatment group.

When the lesions were evaluated for complete healing, it was apparent that BACTODERM treated lesions healed most rapidly. By five days post-treatment, 67% of the lesions were completely healed in the BACTODERM group compared to 43% for the vehicle ointment and 0% for the no-treatment group.

2. Field Study

A clinical field study was initiated to determine the efficacy of BACTODERM Ointment for the topical treatment of skin infections in dogs. A blind, parallel group, multi-center trial was conducted wherein BACTODERM Ointment was compared to the vehicle ointment containing no mupirocin. Animals enrolled in the study were assigned treatment on a random basis with the medication dispensed in coded, identical-appearing tubes according to a sponsor-generated randomization schedule.

Dogs of any breed and either sex with bacterial pustular dermatitis were enrolled in this study. The diagnosis of infection was based upon clinical signs and identification of a pathogen from the pre-treatment culture.

Treatment consisted of cleansing the lesion(s) with a non-antimicrobial solution followed by application of the medication.

A sufficient volume of ointment was applied to cover the affected area twice daily.

Pre- and post-treatment cultures were required in all cases unless healing precluded the availability of post-treatment culture. Clinical symptoms

present at the time of the pre- and post-treatment examinations were described in detail, and in a large number of cases, photographs of the lesions were obtained.

A total of 17 investigators participated in this study. These investigators were located in 11 states and are listed below.

Name	**State**
Drs. James Wilson and Joan Schaeffler	Concord, CA 94520
Dr. Steven Krome	Walnut Creek, CA 94596
Dr. William Cleland	Lilburn, GA 30247
Dr. James Fish	Jacksonville, FL 32210
Dr. Scott Richter	Maretta, Ga 30062
Dr. Dean Small	Overland Park, KS 66204
Dr. Jeri Sill	Omaha, NE 68134
Dr. Robert Cartin	Lakewood, CO 80215
Dr. Ken Kalbfleisch	Nampa, ID 83651
Dr. Joseph Bock	Littleton, CO 80123
Dr. Robert Neunzig	Gatonia, NC 28052
Dr. Lynn Buzhardt	Zachary, LA 70791
Dr. Donald Copeland	Houston, TX 77801
Dr. Sherwood Gill	Lake Charles, LA 70605
Drs. Michael Huddleston and Mark VanNess	Houston, TX 77027
Dr. William Engen	Newberry, SC 29108
Dr. Paul Arnold	Tyler, TX 75701

Overall clinical response was judged according to the following criteria:

Cure: Clinical findings subsided in a reasonable period of time with no evidence of infection at the time drug was discontinued nor during follow-up.

Improvement: Clinical findings subsided significantly in a reasonable period of time but with incomplete resolution of evidence of infection, possible related to underlying disease state.

Failure: No apparent response to therapy.

Of the 57 evaluable pustular dermatitis cases in which *S. aureus* was isolated, 28 were treated with BACTODERM Ointment while 29 were treated with the vehicle ointment. When the clinical response was judged to be a cure or improvement and the bacterial isolate was eliminated, the case was classified as an animal success. A 61% (17/28) animal success rate was observed following treatment with BACTODERM Ointment. The vehicle ointment resulted in an animal success rate of 45% (13/29). BACTODERM® (mupirocin ointment 2%) is identical to the product approved under a New Drug Application (NDA #50-591) for use on humans. Therefore, in accordance with the Center for Veterinary Medicine's Guideline for Effectiveness Evaluation of Topical/Otic Animal Drugs, additional dose determination studies were not required.

B. Corroborative Studies

1. Experimentally Induced *S. aureus* Infection Study

An experimentally induced *Staphylococcus aureus* skin abrasion study was conducted in dogs by Dr. Pat McKeever, University of Minnesota, St. Paul, MN. The purpose of this study was to demonstrate the efficacy of BACTODERM Ointment in reducing the bacterial numbers when compared to the vehicle ointment and a no treatment control. The study was conducted as a double-blind, intra-subject, randomized, parallel design.

A total of nine dogs were used, three replicates of three dogs each. The study compared BACTODERM Ointment, vehicle ointment and a non-treated control. The two medications were packaged and labeled in such a manner as to insure blinding.

The infection procedure involved clipping the hair over the dorsal midline. Abrasions were made to six areas of skin 2.5 cm by 2.5 cm on the back of each dog. A Plexiglas rim was glued to the skin around each lesion. The lesion was then inoculated with 3.25e5 *S. aureus* organisms. The inoculated area was subsequently covered with a coverslip. Twenty-four hours later, quantitative cultures were taken from each site and treatment was initiated. Treatment was applied twice a day for five days. Quantitative cultures were obtained daily prior to treatment.

The total number of bacterial colonies for each treatment group starting 24 hours after the first treatment through 24 hours post-treatment was determined. The BACTODERM Ointment had the lowest count with 2.87e3 followed by the vehicle ointment (3.96e4) and the non medicated control (8.0 e 4).

The bacterial elimination rate is shown in Table #1. Within 24 hours of the first dose, BACTODERM eliminated 94.1% of the original *S. aureus*. The antibacterial effect of mupirocin is apparent when this initial effect is compared to the 47.6% elimination rate for the vehicle and 39.9% for the control.

Table 1 Percent Bacteriological Elimination *S. aureus* (2 cultures/site; 2 sites/dog; 9 dogs)

Treatment	Days of Study -1*	Days of Study -2	Days of Study -3	Days of Study -4	Days of Study -5**
Mupirocin	94.1	96.1	97.7	98.9	99.4
Vehicle	47.6	55.5	88.6	95.4	99.2
Control	39.9	65.4	72.3	84.7	87.1

*24 hours post-first treatment
**24 hours post-last treatment

2. Experimentally Induced Skin Infection Model

A series of experimentally induced skin burn models were conducted in dogs by Dr. Pat McKeever, University of Minnesota, St. Paul, MN. *In vivo* activity against three different pathogens was determined: *S. aureus,* beta-Streptococcus and *E. coli*.

The studies were conducted in a double-blind, intra-subject, parallel, randomized group design wherein BACTODERM Ointment was compared to the vehicle ointment and non-treated controls. Each study consisted of three replicates of four dogs each.

The hair was clipped along the dorsal midline. Six second degree burns 1.9 cm in diameter were made along the back of each dog. The burned areas were scarified and a screw cap container glued to the surrounding skin. The lesions were then inoculated with 1e3 organisms. Treatment was initiated 24 hours later and was continued twice a day for three days. Quantitative bacterial counts were obtained from each site on each dog 12 hours after the last treatment.

The bacteriological efficacy of the treatment was evaluated by the average number of colonies of *S. aureus* per dog for each treatment day and the number of sites per treatment group in which the quantitative count was over 100. The BACTODERM Ointment group had the lowest average count with 77 compared to 549 for the vehicle and 528 for the control. BACTODERM also had the lowest number of sites (3/24) in which the quantitative count was over 100 compared to the vehicle (17/22) and the non-treated control (21/24).

In the second leg of the study, beta-Streptococcus was used to demonstrate *in vivo* antimicrobial activity. The average number of colonies of beta-Streptococcus per dog for BACTODERM was 116 compared to 629 for the vehicle and 755 for the control. In the number of sites in which the colony count was over 100, the BACTODERM Ointment group had the lowest bacterial numbers (7/24) compared to 18 of 24 for the vehicle and 20/24 for the non-treated group.

The third leg of the study utilized *E. coli* as the pathogen. The study design was the same as the previous two studies with the exception that the treatment duration was two days instead of three.

The BACTODERM Ointment group had the lowest average colony count of *E. coli*(27) of the three test groups. The vehicle group had a colony count of 91 and the non-treated group had 186. BACTODERM also had the fewest number of sites in which the *E. coli* count exceeded 100 (2/24) while the vehicle had 18 of 24 and the non-treated group had 20 of 24.

III. ANIMAL SAFETY

A. Pivotal Studies

1. Target Species Chronic Toxicity Study

The objective of this study was to observe any toxic/irritating effects of mupirocin when administered topically to mature dogs for a period of six (6) consecutive weeks. The study was conducted by Dr. M.R. Gilman, LRE, Kalamazoo, Michigan, under the direction of Dr. T.J. Keefe, Beecham Laboratories, Bristol, Tennessee.

Ten male and 10 female adult Beagle dogs were used. Two days prior to treatment the dogs were divided into five groups, each consisting of two males and two females.

This study was an open evaluation of mupirocin utilizing three dosage levels of the test drug (2, 6, and 10%), a placebo group and a control group (no medication). The ointment was administered topically to abraded skin lesions twice a day for six weeks. The following parameters were evaluated: food consumption, temperature, heart rate, respiratory rate, general observations, fecal consistency, body weight, lesion appearance, hematology, clinical chemistry and urinalysis.

The lesions were also evaluated for erythema, swelling and exudate using a scoring system. One male and one female from each group were necropsied on day 43 of the study. The remaining dogs were necropsied on day 44. Gross and histological evaluations were performed.

No values were obtained which were considered to be clinically significant in regard to body temperature, heart rate, respiratory rate, body weight and food consumption.

In regard to the dermal scoring, all levels of test material produced erythema ranging from pink to deep red. The vehicle control and 2% mupirocin produced mild erythema. The non-treated group exhibited a scattered, mild erythema showing some reaction to occlusion. Some edema was observed in all of the test groups initially. With the exception of one dog in the 6% mupirocin group, there was only a scattered incidence of edema after day 26.

Hematology, blood chemistries and urinalysis did not show any consistent pattern of variations. Histopathological examination did not show any meaningful differences in type or severity of reaction at the test article application site between the five groups. All reactions at the application sites were minimal to mild. Any intergroup differences were considered within the range of normal biological variation.

B. Corroborative Studies

1. Acute Toxicity Studies

a. Acute Oral, Subcutaneous and Intravenous Toxicity in the Rat

Acute single dose toxicity studies were conducted with mupirocin sodium by Dr. T.L. Hardy, Beecham Pharmaceuticals Research Division, Harlow, Essex, England.

Three male and three female rats were orally dosed at 5,000 mg/kg. There were no deaths and all animals remained in a healthy condition throughout a 14-day observation period. There were no abnormal findings at the post-mortem examination.

Three male and three female rats were dosed with 5000 mg/kg subcutaneously at a volume of 1 mL/100 g bodyweight. There were no deaths and all animals remained in a healthy condition throughout the 14-day observation period (except for marked injection site irritation). There were no internal abnormalities at post-mortem examination.

Three male and three female rats were used in each of the dose groups discussed below. In dose groups 3200 and 2560 mg/kg, all animals died within 50 to 130 seconds. In dose group 1310 mg/kg, one male and one female died approximately ten minutes after dosing. One female in the 1048 mg/kg dose group died approximately one hour after dosing. One male dosed at 734 mg/kg was found dead on day 14; this death was not considered drug related.

b. Acute Oral Subcutaneous and Intravenous Toxicity in the Mouse

Acute single dose toxicity studies in the mouse were conducted with mupirocin sodium by Dr. T.L. Hardy, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. The mice were observed for 14 days. In the subcutaneously and intravenously dosed mice, the kidneys were thought to be possible target organs.

2. Subacute and Chronic Studies

a. Topical Repeat Dose Study

Sixty-five male and 65 female rats were allocated to five treatment groups of 10 males and 10 females per group with an additional five animals of each sex in the high dose and control groups. Mupirocin ointment was administered topically to areas of shaved skin at dose levels of 10, 20 and 40 mg/kg. Animals were dosed with 2 ml/kg of the vehicle ointment alone and the other group remained undosed.

At the end of the 28 day treatment period, 10 animals from the high dose group and ten from each of the control groups were left undosed for a withdrawal period of 14 days.

The treatment area of each rat was observed daily for erythema, eschar and edema formation. After 28 days of treatment and after 14 days 'off-dose' as appropriate, the rats were sacrificed an subjected to a detailed post-mortem examination.

There were no mortalities and no apparent local reaction to treatment. Hematological examination revealed no changes considered to be treatment related. No treatment related changes were found on organ weight analysis or macroscopic pathological examination. Histopathology showed a dose related incidence of parietal cell vacuolation in the stomachs of treated females which was not present after the 14 day regression period. No evidence of a reaction to treatment was seen at the application sites. This study was conducted by Drs. A. Cockburn and D.J. White, Beecham Pharmaceuticals Research Division, Harlow, Essex, England.

b. Oral and Subcutaneous Repeat Dose Study

A 14-day repeat study in the rat was conducted with mupirocin sodium by Dr. T.L. Hardy, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Fifty male and 50 female rats were allocated to five treatment groups of 10 male and 10 female rats per group, plus an additional group of five male and five female rats left undosed. Mupirocin sodium was administered subcutaneously at levels of 100 and 500 mg/kg and orally at 100 mg/kg. Controls received distilled water for the orally dosed rats and sterile saline for the rats dosed subcutaneously. Dosing was carried out daily for 14 consecutive days.

There were no treatment related deaths. Animals receiving 100 mg/kg orally and subcutaneously showed no adverse external signs. At 500 mg/kg subcutaneously, all animals had injection site pathology after three doses. There was no adverse effects on the body weights and no treatment related changes were seen in food and water intake or feed conversion.

Hematological examination showed that rats receiving the 500 mg/kg subcutaneous dose had a slight decrease in hemoglobin, PCV and red cell count, together with an increase in total leukocyte count and absolute neutrophil count. Orally dosed females had slightly increased hemoglobin and red cell counts with a decreased MCV.

Blood chemistries showed that rats receiving the 500 mg/kg subcutaneous dose had reduced SAP activity, total protein, albumin and A/G ratio together with increased ALT activity. Males also exhibited increased glucose and decreased potassium levels. Orally dosed rats exhibited no changes considered treatment related.

Post-mortem examinations revealed injection site pathology. Histopathologic exam revealed a marginal increase in changes in the kidneys when compared with controls in four of 12 animals receiving the high subcutaneous dose and two of 12 animals receiving the oral dose. A

dose related increase was also seen in the extent and severity of subcutaneous injection site reactions.

c. Subcutaneous Repeat Dose Study

A three-month subcutaneous repeat dose study in rats was conducted with mupirocin sodium by Drs. A. Cockburn and D.J. White, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Seventy males and 70 female rats were allocated to four treatment groups of 15 males and 15 females per group, with an additional five males and five females in control and high dose groups. Mupirocin sodium was administered subcutaneously at dose levels of 10, 40 and 100 mg/kg. All animals were dosed for a minimum of 90 days; at the end of dosing, five males and five females from the control and high dose groups were left undosed for a withdrawal period of 28 days. At the end of the treatment or withdrawal period, all animals were sacrificed and detailed post-mortem examination performed.

There were no treatment related deaths with the exception of one female in the 100 mg/kg group which was killed *in extremison* Day 3 having been found in poor condition. Treatment related alopecia and/or scab formation at all injection sites was seen from Day 7 in the high dose group.

Hematological examination showed no significant changes except for a slight reduction in red cell parameters in treated females at the interim examination. Blood chemistries showed a slight increase in ALT in intermediate and high dose males at the terminal examination. Histopathological examinations showed no changes considered to be related to treatment.

d. Repeat Dose Dermal Toxicity Study

A 30-day repeat dose dermal toxicity study in the rabbit was conducted with mupirocin by Dr. P. Varney, Hazleton Laboratories, Harrogate, North Yorkshire, England. Thirty-one male and 31 female rabbits were allocated to five treatment groups of five males and five females per group with an additional two animals of each sex in the high dose and control groups. Mupirocin ointment was administered topically to areas of shaved, abraded skin at dose levels of 10, 20 and 40 mg/kg. One control group was dosed with the vehicle at 2 ml/kg and the other control group remained untreated. Doses were applied daily for 30 days, each dose remaining on the skin under an occlusive dressing for a six-hour period.

There were no treatment-related deaths or clinical signs. No treatment-related changes in any of the hematologic or blood chemistry parameters were evident. At the post-mortem examination, there were no macroscopic changes considered treatment related. Histopathologic examinations revealed minimal acanthosis of the epidermis and/or minimal leukocyte accumulation in the stratum corneum at the treatment site in both the vehicle control and high dose test animals.

There were no findings in the other tissues examined to suggest an effect of treatment.

e. Maximum Tolerated Subcutaneous Dose in Rabbits

A maximum tolerated dose study was conducted in rabbits by Dr. A. Cockburn, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Mupirocin sodium was administered to five female rabbits by the subcutaneous route in order to ascertain the maximum tolerated dose. Treatment commenced at 20 mg/kg and the dose was doubled at three day intervals until a level of 640 mg/kg had been achieved. Five female rabbits receiving sterile saline subcutaneously served as controls. At the end of the dosing period, those animals treated with mupirocin sodium were sacrificed and subjected to a detailed macroscopic examination.

There were no mortalities. Signs of irritation were apparent following treatment at 20 and 40 mg/kg. Two rabbits showed evidence of darkened urine at 80 mg/kg. On terminal examination, subcutaneous hemorrhages were seen at the injection sites. This study suggests that the maximum tolerated subcutaneous dose of mupirocin sodium in rabbits is greater than 640 mg/kg.

f. Subacute Oral and Intramuscular Toxicity

A study of the subacute (14 day) toxicity of mupirocin sodium administered by the oral and intramuscular routes to squirrel monkeys was conducted by Dr. B.G. Procter, Beecham Pharmaceuticals Research Division, Harlow, Essex, England.

Each of five study groups consisting of two male and two female squirrel monkeys and the test animals received mupirocin sodium by either the oral or intramuscular route. In both cases, two dose levels (50 and 150 mg/kg) were investigated. Control animals received sterile saline via the intramuscular route.

There were no mortalities during the study and no signs of adverse effects of treatment on the appearance or behavior of the animals. No treatment related effects were seen on body weight or food consumption.

At necropsy, no treatment related effects were seen. Comprehensive histopathological examination of tissues and bone marrow revealed no definite systemic toxic effects. Focal reactive inflammation and edema was observed at the injection site.

g. Maximum Tolerated Oral and Intramuscular Dose in Squirrel Monkeys

A maximum tolerated dose study was conducted in squirrel monkeys by Dr. J. Hopkins, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Mupirocin sodium was administered to three male and

three female squirrel monkeys which were allocated to three groups of one male and one female per group. The mupirocin sodium was administered for four days at each of the following incremental dose levels: 100, 250, 500, 1000 and 2000 mg/kg. At the end of the treatment period, all animals were killed and subjected to a detailed post-mortem examination.

There were no mortalities. One hematological examination revealed decreased red blood cell values with anisocytosis from Day 9 onward in the female monkey dosed intramuscularly. Blood chemistries revealed that SAP activity was variable in controls and orally treated monkeys. SGPT became elevated compared with pre-dose values in both of the animals treated intramuscularly and the BUN was slightly elevated in the male IM monkey at term. Post-mortem examination revealed no abnormalities other than a change in liver color. Histological abnormalities considered to be related to treatment included very minimal fatty change in the liver of the two monkeys dosed orally. In both monkeys dosed by the intramuscular route, there was minimal fat deposition in the livers, mild tubular dilation in the kidneys and moderate inflammatory changes at the injection site.

The maximum tolerated dose for mupirocin sodium in the squirrel monkey was therefore greater than 2000 mg/kg when given orally and between 1000 and 2000 mg/kg when given intramuscularly.

h. Repeat Dose Toxicity in Dogs

A three-month intravenous repeat dose study in Beagle dogs with a 28-day off-dose period was conducted by Drs. A. Cockburn and D.J. White of Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Twenty male and 20 female Beagle dogs were allocated to four treatment groups of four males and four females per group with an additional two males and two females in the control and high dose groups. Mupirocin sodium was administered intravenously at dose levels of 5, 10 and 20 mg/kg (reduced from 10, 40 and 80 mg/kg on Day 4). The control group received sterile saline under identical conditions. All animals were dosed for a minimum of 91 days; two males and two females from the control and high dose group were left undosed for a withdrawal period of 28 days.

There were no deaths, but immediate and severe reaction to treatment (in particular, muscular weakness, convulsions or ataxia) was evident in several dogs at levels of 40 and 80 mg/kg. On lowering of these dose levels to 10 and 20 mg/kg, a reaction continued to be elicited until a reduced injection rate was introduced for the affected animals on day 7. Apart from two isolated incidences in these dogs and in an additional high dose dog showing reaction to treatment after 27 days, there were no further adverse signs. All other dogs remained unaffected by treatment.

Body weight, food and water intake were all unaffected by treatment.

Hematological analysis revealed a decrease in total leukocyte counts in most intermediate and high dose males and the majority of females from all treated groups. Blood chemistry tests showed an increase in A/G ratio in four high dose males at terminal examination.

Neither urinalysis nor ophthalmological examination revealed any changes considered to be related to treatment.

Macroscopic pathology, histopathology and organ weight analysis showed no changes which were considered to be related to treatment.

3. Reproduction and Teratology Studies

a. Preliminary Teratology Study in the Rat

A preliminary teratology study in the rat was conducted with mupirocin sodium by Dr. T.L. Hardy, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Fifty-four female rats were allocated to four groups of 12 animals each and one group of six animals. Mupirocin sodium was dosed subcutaneously at 100, 250 and 500 mg/kg beginning on day six of the gestation, but the highest dose level was reduced to 375 mg/kg after the first dose due to severe injection site reactions. The compound was administered from days 6-15 of gestation inclusive. Control animals were treated with sterile saline under identical conditions. On day 21 of gestation, the animals were sacrificed and subjected to an internal macroscopic examination. There were no mortalities and clinical signs were restricted to localized tissue reactions at the injection site. There were no significant differences between mupirocin sodium treated and control animals in regard to pregnancy rate, litter size, pre- and post-implantation losses, fetal and litter weights and fetal sex ratios.

b. Effects of Subcutaneous Administration of Mupirocin Sodium on Pregnancy in Rats

A study was conducted to determine the effects of subcutaneous administration of mupirocin sodium on the course and outcome of pregnancy in rats by Dr. A. Cockburn, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. One hundred twelve premated female rats were randomly allocated to four treatment groups of 28 animals. Dosing of mupirocin sodium at 10, 40 and 200 mg/kg and sterile saline as control was initiated on day six of gestation, but the high dose level was reduced to 160 mg/kg after the first dose due to marked injection site irritation. The compound was administered subcutaneously from days six to 15 of gestation inclusive. Control animals received sterile saline under identical conditions. On day 21 of gestation, all surviving animals were sacrificed and a detailed macroscopic post-mortem examination was conducted.

Mupirocin sodium when administered subcutaneously daily through the main period of organogenesis at doses up to 160 mg/kg produced no

overt toxicity or evidence of any adverse effects on the growth and development of offspring *in utero*.

c. Effect of Mupirocin Sodium on Peri- and Post-Natal Development of Rats

A study was conducted to determine the effects of subcutaneous administration of mupirocin sodium on the peri- and post-natal development of rats. This study was conducted by Dr. A. Cockburn, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. On day 14 of gestation, animals were allocated into four treatment groups containing 22 rats. Mupirocin sodium was administered subcutaneously at dose levels of 11.1, 44.2 and 106.7 mg/kg from Day 15 of gestation to Day 25 *post-partum* inclusive. Control rats received sterile saline under identical conditions.

Mupirocin sodium had no effect on peri- and post-natal development at dose levels up to and including 44.2 mg/kg. Pup survival was reduced in some litters given 106.7 mg/kg, but the majority of litters was unaffected. Other aspects of offspring development were normal at this dose level.

d. Fertility and General Reproductive Performance of Rats

A study was conducted to determine the effects of mupirocin sodium on fertility and general reproductive performance of rats. This study was conducted by Dr. A. Cockburn, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. The animals were allocated in four treatment groups each containing 28 male and 28 female rats. Mupirocin sodium was administered subcutaneously at dose levels of 10, 40 and 100 mg/kg. The control group of animals received sterile saline under identical conditions. Male rats were dosed for ten weeks before pairing throughout the mating period and until successful littering was achieved by the females. Females were dosed for 15 days before pairing throughout the mating period and through day 20 *post coitum*. For those animals killed on Day 21 *post coitum*, and in the case of animals allowed to litter, dosing continued throughout the littering and lactation period until Day 24 *post partum*.

F0 Generation

Animals receiving 40 and 100 mg/kg showed signs of local irritation at the injection site. Estrus cycles, mating performance, fertility and gestation lengths did not vary with treatment. In animals allowed to litter naturally, litter size, viability, growth and development of the young to weaning remained unaffected by treatment. At termination, no signs of macroscopic internal pathologic changes in males, females or offspring were found. It was concluded that treatment with mupirocin sodium at dose levels of up to 100 mg/kg is without significant effects of reproductive performance of the F0 generation.

F1 Generation

Some effects on F1 female body weight gain at dose levels of 10, 40 and 100 mg/kg were recorded but these appeared to have no consequences in terms of reproductive performance. At 100 mg/kg there was a suggestion of slightly reduced recall ability in the F1 males. At the same dose, female offspring had a significantly reduced performance in the righting reflex test. In all other respects, development was essentially normal with no indication of effects on the part of mupirocin sodium.

e. Effects on Pregnancy of Rabbits

A study in rabbits was conducted with mupirocin sodium by Dr. T. L. Hardy, Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Sixty premated female rabbits were divided into four groups each containing 15 animals. Mupirocin sodium was administered subcutaneously at dose levels of 10, 40 and 160 mg/kg daily from Day 6 to Day 18 of pregnancy. Control animals received physiological saline under identical conditions. On Day 29 of pregnancy, the animals were sacrificed and subjected to extensive post-mortem examination. Four animals at the 160 mg/kg dose showed injection site reactions. Three of these animals aborted and were killed before day 29 of pregnancy because of poor condition. In addition to these animals, one control animal and one dosed at the 160 mg/kg aborted. The abortions in the high dose group animals were clearly related to the poor general condition of the animals.

There was no evidence of an adverse treatment related effect on the incidence of major malformations, minor anomalies or skeletal variance.

4. Mutagenicity Studies

A series of mutagenicity studies have been conducted by Beecham Pharmaceuticals Research Division, Harlow, Essex, England. In bacterial tests, conventional AMES agar plate assays have proved negative. In *S. typhimurium*, TA98 in liquid culture and in a 'repair' test with *E. coli* very small responses, around 2-3 fold the control values, have occurred in the absence of metabolic activity. These effects have been reported for other antibiotics whose mode of action is inhibition of protein synthesis.

Tests in higher organisms (i.e., yeast, mammalian cell culture, analysis of human chromosomes *in vitro* and a micronucleus test in the mouse of *in vivo* damage), no mutagenic effects have been seen. The latter tests have been conducted using very high concentrations of the compound in relation to the likely animal exposure.

5. Miscellaneous Studies

a. Eye Irritation Studies in the Rabbit

A study was conducted by Hazleton Laboratories, Harrogate, North Yorkshire, England, to determine the eye irritation in the rabbit. In this

study, three groups of three animals received 2% mupirocin in the left eye. The eyes of one group remained unrinsed after instillation, those of the second group were irrigated after two seconds and the eyes of the third group were irrigated after four seconds. The untreated right eye of each animal served as a control.

Mupirocin did not appear to cause any initial pain on instillation in the eye. No iridal inflammation nor corneal opacity were seen during the study. Based upon the results of this study, mupirocin in polyethylene glycol was classified as non-irritating to the rinsed eye and as practically non-irritating to the unrinsed eyes of rabbits.

b. Primary Skin Irritation in the Rabbit

A study to determine the primary skin irritation in rabbits was conducted by Hazleton Laboratories, Harrogate, North Yorkshire, England. Six rabbits were used in this study. An area on the back of each animal was clipped. The left side of the clipped area was left intact and the right side was abraded. Two percent mupirocin ointment was applied to both skin sites and covered with gauze pads.

No adverse skin reactions were noted at either the 24 or 72-hour observation. A primary irritation index of 0 was obtained, thus, it was concluded that a single 24-hour application of mupirocin in polyethylene glycol ointment to occluded rabbit skin was non-irritating.

c. Immunogenicity Studies in Laboratory Animals

Intradermal sensitization studies in rats and contact sensitization studies in guinea pigs were conducted with mupirocin by Beecham Pharmaceuticals Research Division, Great Burgh, Surrey, England.

Twelve rats were allocated into groups of six animals. One group received a subcutaneous dose of 10 mg of mupirocin in Freund's complete adjuvant and six intradermal doses of 1 mg of mupirocin in buffered saline. The control group received the same volumes of the vehicles only. The animals were challenged 14, 21 or 28 days after the sensitizing dose.

No erythema, induration or other adverse reactions were observed in animals up to 48 hours after challenge at 14, 21 or 28 days after sensitization. Mupirocin did not, therefore, induce cellular immunity in rats.

Twelve male guinea pigs were allocated in two groups. One group was treated with 100 mcl of a 0.1 molar solution of mupirocin applied topically to the shaved flank. The other group was treated with the vehicle only. In each case, a total of six applications in 12 days were made to the same site. Animals were challenged 23 days after the first sensitizing dose on two sites on the contralateral side. No erythema or adverse reactions were observed in any of the sites tested in either

group up to 48 hours after challenge. Mupirocin was not considered irritant nor a contact sensitizing agent under these conditions.

Eighteen female guinea pigs were allocated in three groups of six animals. One group was treated with a 0.3 molar solution of mupirocin, a second group was treated with 3% oxazolone solution as a positive control and the third group was treated with the vehicle alone. One hundred microliters of the respective solutions were applied topically to a site on the shaved flank six times during a 12-day period. Animals were challenged 4, 6, 10 and 18 weeks after the first sensitizing dose.

Mupirocin had no local irritant effect on the skin. Four animals produced a low level response to the highest challenge concentration although evaluation of this response was complicated by a generalized erythema. Mupirocin provoked a more pronounced response at the second challenge, but in subsequent challenges, it caused a weak response in only one animal. From these studies, mupirocin is considered to be a weak contact sensitizing agent in the guinea pig.

d. Modified Draize Skin Sensitivity Study in the Guinea Pig

A skin sensitization study in the guinea pig (modified Draize method) was conducted with mupirocin by Hazleton Laboratories, Harrogate, North Yorkshire, England.

No adverse skin reactions were observed during the induction period. Five of the animals previously induced with 2% mupirocin ointment showed very slight erythema 24 hours following the challenge application. No edema was noted at this time. The skin response regressed and a very slight erythema was noted in only one animal after a further 24 hours.

These results indicate that mupirocin has some sensitizing potential in the guinea pig.

e. Cardiovascular Toxicity Studies in Dogs

A cardiovascular toxicity study in anesthetized Beagle dogs with mupirocin sodium was conducted by Beecham Pharmaceuticals Research Division, Harlow, Essex, England. Two male and one female Beagle dogs were anesthetized and set up to measure systemic blood pressure and heart rate. Mupirocin sodium was administered intravenously to the animals at a dose volume never exceeding 1 ml/kg body weight. One male and one female animal were given ascending doses of mupirocin sodium at 30 minute intervals to assess the effect of increasing doses on cardiovascular parameters. The male dog received doses of 5, 12.5, 25, 50 and 100 mg/kg; the female dog was dosed additionally at 2.5 mg/kg. The third animal was dosed with the same lot of mupirocin sodium as the other two animals at 25 mg/kg and the effect was compared to that of doses of 20 and 25 mg/kg of a new lot of mupirocin sodium.

Mupirocin sodium at 5 mg/kg had no effect on heart rate or blood pressure. The 12.5 and 25 mg/kg doses caused hypotension and bradycardia. Increasing the dose to 50 or 100 mg/kg had no greater effect than the 25 mg/kg dose. The changes in heart rate and blood pressure were rapid in onset (within approximately one minute of dosing) and were spontaneously reversible within six minutes. ECG recordings revealed no abnormalities of wave form.

f. Local Irritancy Study in Rats

A local irritation study in the rat was conducted by Beecham Pharmaceutical Research Division, Harlow, Essex, England.

Mupirocin sodium in sterile water was injected intramuscularly into the shaved right thigh of rats at a concentration of 25 mg/2 ml or 250 mg/2 ml at a dose volume of 0.2ml. Rats were given either one or seven daily injections followed by one or seven days recovery. Sterile water was injected into the left thigh muscle under identical conditions to act as control.

There was no apparent effect of treatment on the general clinical appearance of any of the rats in the study. A dose related injection site reaction was evident in these animals.

g. Effect of Mupirocin on Wound Healing in Pigs

A study was conducted to determine the effect of mupirocin on epidermal wound healing in pigs by Dr. William H. Ealgstein, University of Pittsburg, Pittsburg, PA. Young domestic pigs were clipped and shaved. Approximately 100 rectangular wounds were made in the paravertebral and thoracic area with a Castroviejo Keratome. Daily thereafter for seven days, the wounds on each back were treated with either mupirocin ointment, vehicle or received no treatment.

By day 5, 100% of the wounds treated with either mupirocin ointment or its vehicle were healed as compared to 27% of the untreated wounds. By day 6, all untreated wounds had also healed. Thus, neither mupirocin ointment nor its vehicle produced any inhibition of epidermal wound healing.

IV. HUMAN SAFETY

Human Safety:

A. Human Safety Relative to Food Consumption

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This product is labeled as a prescription drug for use only on dogs, which are non-food animals**.**

B. Human Safety Considerations Other Than Food Safety

No special human caution statement is needed.

V. AGENCY CONCLUSIONS

The data submitted in support of this New Animal Drug Application (NADA) comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrated that BACTODERM (mupirocin), when used under its approved conditions of use, is safe and effective for the topical treatment of canine bacterial infections of the skin, including superficial pyoderma, caused by susceptible strains of *Staphylococcus aureus* and *Staphylococcus intermedius*.

This product is prescription because the expertise of a veterinarian is necessary for diagnoses of the underlying etiologies resulting in the conditions for which the product is indicated.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.