Approval Date: June 9, 1993

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-896

B. Sponsor

Schering-Plough Animal Health Corporation
P.O. Box 529
Kenilworth, New Jersey 07033

C. Proprietary Name

OTOMAX®

D. Established Name

Gentamicin sulfate, clotrimazole, and betamethasone valerate

E. Dosage Form

An ointment

F. Dispensing Status

OTC, Rx, or VFD

G. Dosage Regimen

Administer 4 drops (2 drops from the 215 g bottle) for dogs weighing 30 pounds or less and 8 drops (4 drops from the 215 g bottle) for dogs weighing over 30 pounds, twice a day for seven days.

H. Route of Administration

applied directly into infected ears.

I. Indication

OTOMAX is indicated for treatment of canine acute and chronic otitis externa associated with yeast (*Malassezia pachydermatis*formerly *Pityrosporum canis*) and/or bacteria susceptible to gentamicin.

II. EFFECTIVENESS

The combination of gentamicin (3.0 mg/g) and betamethasone (1.0 mg/g), as found in Topagen, with clotrimazole (10 mg/g) provides a single product indicated for use in the treatment of acute and chronic otitis externa in the dog associated with bacteria susceptible to gentamicin and/or yeast (*M. pachydermatis/Pityrosporum canis*).

Pivotal Studies

A. Component Efficacy Study (C-6-87)

Name and Address of Investigator:

A.M. Benitz, D.V.M.
Schering Corporation
Schering Animal Health
P.O. Box 608
Allentown, N.J. 08501

General Design of the Investigation:

1. Purpose:

To establish the component efficacy of OTOMAX.

2. Test Animals:

Species: Canine, beagle
Number of Animals: 28
Age Range: Young adult or adult
Weight Range: 15-28 lbs.
Sex: Mixed
Acclimation: 2 weeks
Supplier: Schering Toxicology Labs, Lafayette, N.J.
Diet: Purina 5006, water *ad libitum*

3. Test Articles:

1. OTOMAX: gentamicin 3.0 mg/g, betamethasone 1.0 mg/g, and clotrimazole 10 mg/g.
2. Clotrimazole: clotrimazole 1% (10 mg/g)
3. TOPAGEN: gentamicin 3.0 mg/g and betamethasone 1.0 mg/g in mineral oil vehicle.
4. Placebo: OTOMAX formulation vehicle.

4. Treatment Schedule:

Otitis externa was induced in twenty-eight dogs using *Staphylococcus aureus*and the yeast, *Malassezia pachydermatis*. Dogs were randomly assigned into 4 treatments groups. Treatment began after induction of acute otitis externa and assignment into groups.Treatments were given according to the label instruction for TOPAGEN Ointment, i.e., 4 drops per treatment (for dogs less than 30 pounds), administered twice a day for 7 days. Following instillation of drug, the ear was gently massaged to ensure full, even distribution of the drug.

Blinding was accomplished by serially numbering each treatment tube. Each dog was assigned a single numbered tube immediately prior to the first treatment. The number code was broken at the conclusion of the trial.

5. Study Duration:

11 days

6. Parameters Measured:

Clinical:
1. Discomfort
2. Inflammation (i.e., erythema)
3. Swelling
4. Exudate - odor, color, quantity

Microbiological Agar plates containing selective media for bacteria or fungi were inoculated from ear swabs taken from each dog at each observation point. Resulting growth was scored for relative amounts of bacteria and or *M. pachydermatis*. In addition, ear swabs were used to make a roll smear which was evaluated for relative numbers of bacteria and *M. pachydermatis*cells.

7. Summary of Results

OTOMAX adequately controlled the clinical signs associated with an induced otitis externa and effectively eliminated both the bacterial and *M. pachydermatis*infections, although there was still evidence of bacterial and yeast growth on roll smears and in culture. Significant improvement in clinical signs was seen by the first post-treatment observation (Day 4). OTOMAX was most effective in eliminating both bacterial and *M. pachydermatis* infections. OTOMAX was not different from TOPAGEN and both were superior to placebo and clotrimazole in controlling clinical signs and eliminating bacterial infections.

8. Statistical Analysis:

The variables discomfort, swelling, and odor were analyzed by Fisher's Exact Test. The variables inflammation and quantity of exudates were analyzed by Ridit Analysis. Cultures from the ears of each dog were grown on four selective media. Resultant growth was rated. Ridit analysis was used to analyze the results from each medium. Roll smear results were ranked for each observation, then analyzed by a Kruskal-Wallis test.

All of the above analyses were performed separately for each observation day. Statistical significance was declared at the $p <= 0.05$ level.

For the clinical observations, no significant differences between groups were observed on day 1, indicating comparable infections in all four groups. At the later time points, OTOMAX and TOPAGEN were clinically superior to the Placebo or Clotrimazole groups. No clinical differences were seen between OTOMAX and TOPAGEN as both products contain betamethasone which rapidly controlled signs of inflammation.

For the microbiology culture observations, all groups were comparable on day 0 and day 1. For the Sabouraud's plate, the OTOMAX group had significantly lower culture scores than the Placebo and TOPAGEN groups on day 4 and day 8. At later dates, the OTOMAX group had significantly lower culture scores

than the Placebo and Clotrimazole groups on blood and mannitol salt plates, but no difference was seen on McConkey agar.

OTOMAX and Clotrimazole groups had significantly reduced *M. pachydermatis* roll smear counts over TOPAGEN and Placebo groups. The Clotrimazole group, however, did not demonstrate a statistically significant difference for *M. pachydermatis*over Placebo with regard to agar growth scores.

9. Conclusion:

It was concluded that OTOMAX was effective in controlling the clinical signs associated with an induced mixed bacterial and *M. pachydermatis*otitis externa. The safety and compatibility of the components of OTOMAX was demonstrated. OTOMAX was determined to be better than Placebo or Topagen for yeast culture scores on days 4 and 8. OTOMAX and Clotrimazole were determined to be better than Placebo or Topagen for roll smear results for yeast. However, Clotrimazole was not determined to be better than Placebo for yeast culture scores. Due to the ambiguous nature of results regarding the efficacy of the clotrimazole component, an additional study was required to confirm the efficacy of 1% clotrimazole (V89-010).

10. Adverse Effects:

No adverse effects were observed during this study in any of the dogs receiving either OTOMAX, TOPAGEN, or Placebo.

B. Efficacy of Clotrimazole in Experimentally Induced Canine Otitis Externa (V89-010)

Name and Address of Investigator:

Ross D. Lobell
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General Design of the Investigation:

1. Purpose:

To determine the efficacy of 1% clotrimazole compounded in the OTOMAX vehicle versus OTOMAX vehicle in an experimentally induced *Malassezia pachydermatis*otitis externa in dogs.

2. Test Animals:

Species: Canine, mixed breeds
Number of Animals: 36
Age Range: Young Adult or Adult
Weight Range: 27 to 54 lbs.
Sex: Mixed
Acclimation: One Week

3. Test Articles:

   a. OTOMAX Vehicle

   b. Clotrimazole 1% (10 mg/g) in the OTOMAX vehicle.

4. Treatment Schedules: Thirty-six dogs with an experimentally induced *Malassezia pachydermaris*otitis externa were randomly assigned into two groups. Treatments were administered according to the label instructions for OTOMAX.

5. Study Duration: 10 days

6. Parameters Measured:

   Clinical:
   1. Discomfort
   2. Swelling
   3. Inflammation
   4. Exudate - odor, color, quantity

Microbiological: Amounts of *M. pachydermatis*in the affected ear were monitored and quantitatively scored on Sabouraud's Dextrose Agar.

7. Summary of Results:

   Clotrimazole treated dogs demonstrated a statistically significant reduction in *M. pachyderrnatis*infection levels over placebo treated dogs on Study Days 3, 5, 7 and 10. By Day 10, the organism was eliminated in 88% of the dogs receiving clotrimazole while all of the dogs receiving the placebo remained positive for the organism.

8. Statistical Analysis:

   Infection levels of *M. pachydermaris*and the clinical parameters of discomfort, swelling, inflammation, exudate quantity and color were analyzed by the Wilcoxon Midrank Test. Exudate odor was analyzed by Fisher's Exact Test. Statistical significance was declared at the $p <= 0.05$ level.

   The comparisons of the *M. pachydermaris*scores between Clotrimazole and Placebo groups were not statistically significant on Day 1 or Day 0. The differences in the *M. pachydermaris*growth scores between the clotrimazole and placebo groups were statistically significant on all other examination days (Days 3, 5, 7, and 10).

   There was no evidence that the two treatment groups differed with respect to level of discomfort at any of the scheduled assessments. Swelling was significantly reduced in the clotrimazole group, over Placebo, on Days 7 and 10. Inflammation scores were also significantly improved in the clotrimazole group as compared to Placebo on Day 7. There was no statistically significant difference with respect to the quantity or color of exudate at any of the observations. The exudate odor was significantly less evident in dogs treated with clotrimazole on Days 5, 7, and 10.

9. Conclusions:

Clotrimazole at a concentration of 1% in the OTOMAX vehicle demonstrated a statistically significant effect over OTOMAX vehicle alone in elimination of *M. pachydermatis*from the ear. Clotrimazole also exerted a statistically significant effect on exudate odor and swelling.

10. Adverse Effects:

No adverse reactions attributable to treatment were encountered during the course of the study. Two dogs died during this study - one in the clotrimazole group and one in the control group. Necropsy and histopathology revealed no definite cause of death in the dogs; however, a clinical diagnosis of viral enteritis was made. This was based on an outbreak of similar signs affecting several animals from both groups, of which all but two recovered.

Both studies C-6-87 and V89-010 are pivotal in establishing the component efficacy of OTOMAX. In study C-6-87 the three way combination of betamethasone valerate, gentamicin sulfate, and clotrimazole was shown to be superior to either the two way combination of betamethasone valerate and gentamicin (TOPAGEN) or clotrimazole alone for treatment of otitis externa in dogs caused by bacteria susceptible to gentamicin and/or *M. pachydermatis*. Study V89-010 demonstrated that 1% clotrimazole was superior to placebo against experimentally induced *Malassezia pachydermatis*(yeast). The combination product is therefore justified. The TOPAGEN components, betamethasone valerate and gentamicin sulfate, contribute to the treatment of acute and chronic canine otitis externa caused by bacteria susceptible to gentamicin. The clotrimazole 1% component contributes to the treatment of acute and chronic canine otitis externa associated with *M. pachydermatis*.

C. Positive Controlled Clinical Evaluation (V87-008)

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General Design of the Investigation

1. Purpose:

   To compare the safety and efficacy of a clotrimazole-gentamicin betamethasone (OTOMAX) combination otic product with a commonly prescribed FDA-approved product with similar claims (Panolog Ointment), in a blinded and randomized fashion, under clinical conditions of use.

2. Test Animals:

   Species: Canine, multiple breeds
   Number of Species: 58
   Age Range: <1 -18 years
   Weight Range: 3-140 lbs.
   Sex: Mixed

3. Test Articles:

   a. OTOMAX: 10 mg/g clotrimazole, 1.0 mg/g betamethasone valerate, and 3.0 mg/g gentamicin sulfate
   b. Panolog Ointment: commercially available

4. Treatment Schedule:

   Dogs from each center in the U.S. were randomly assigned into the two treatment groups. Centers represented three distinct geographic regions.

   A total of 341 dogs of various breeds, ages, weights, and both sexes were presented for diagnosis and treatment of otitis externa with both bacterial and *M. pachydermatis*infections. There were 58 cases which met the inclusion criteria and these were subsequently included in this study. Dogs with ear mite infestations were excluded as well as those receiving concomitant local or systemic antibiotic therapy. Concomitant therapy for unrelated disorders such as diabetes, congestive heart failure, etc., was permitted.

   Previous treatment and cultural history were obtained wherever possible. A complete physical and otoscopic examination was made of both ears in each affected animal included in the study.

   Dogs enrolled in the study were assigned to a treatment group, with the medication dispensed in coded, identically-appearing tubes, according to a sponsor-generated randomization schedule. To further ensure blinding, treatment was administered by someone other than the principal investigator.

Prior to inclusion in the study the ear was swabbed and a roll smear was made to demonstrate both bacteria and *M. pachydermatis*were present and were believed to be contributing to the otitis externa. A dog was eligible for inclusion whether one or both ears were affected. In cases where the infection was bilateral both ears received the same treatment, but only the right ear was included for evaluation of treatment.

The first microbiology specimen was collected and clinical evaluation was made prior to initiation of treatment. The ears were cleaned with an ear cleansing solution free of antimicrobial and anti-inflammatory activity. Medication was applied twice daily for seven days according to label instructions:

a. Dogs that weighed 30 lbs. or less received 4 drops per affected ear.
b. Dogs that weighed more than 30 lbs. received 8 drops per affected ear.

After treatment the ears were massaged, taking care to distribute the medication evenly throughout the ear canal.

A second examination was made 2 - 4 days following termination of treatment at which time the ears were examined clinically and microbiologically as before.

Cases which did not complete the full 7-day therapeutic regimen and reexamination were considered dropouts. The dropouts were analyzed as described in the statistical section.

5. Study Duration:

9-11 days

6. Parameters Evaluated:

Clinical
1. Discomfort
2. Inflammation
3. Swelling
4. Exudates-quantity, color, odor

Microbiology
1. Gram-stained smears
2. Culture
3. Sensitivity

7. Summary of Results:

OTOMAX adequately controlled the clinical signs associated with otitis externa. In addition, OTOMAX controlled both bacteria and *M. pachydermatis*infections associated with otitis externa. OTOMAX was safe when applied to dogs' ears for the treatment of otitis externa.

8. Statistical Analysis:

A total of 58 cases qualified for inclusion in the statistical analysis. Data were pooled across the five investigators supplying qualified cases.

The continuous variable, weight, was analyzed by Analysis of Variance. Categorical variables, sex, otitis duration, otitis type, affected ear, discomfort, swelling, exudate color and odor, otitis resolution and elimination of *M. pachydermatis*, were analyzed by Fisher's Exact Test. Ordered categorical variables, age, inflammation, exudate quantity, overall evaluations by investigator, owner and microbiologist, and quantitative assessment of roll smear results, were analyzed by Wilcoxon Midrank Test. Statistical significance was declared at the $p <= 0.05$ level.

There were no statistically significant differences between OTOMAX and Panolog Ointment groups for weight, age, sex, otitis duration, otitis type, affected ear, discomfort, inflammation, swelling, exudate quantity, exudate odor, overall evaluation by the investigator, microbiologist and owner. OTOMAX and Panolog both reduce the quantity of *Malassezia*spp. found on fungal roll smears.

Culture results showed that Panolog eliminated a significantly greater number of *Staphylococcus*spp. (3 of 3) than OTOMAX. Otherwise roll smear and culture results were not statistically different with regard to bacteria.

9. Conclusion:

This controlled clinical study demonstrated that OTOMAX, a combination (clotrimazole-gentamicin-betamethasone) otic product, administered to dogs as recommended was equivalent, with regard to adverse reactions or side effects, to the approved product (Panolog Ointment).

OTOMAX significantly reduces the quantity of *Malassezia*spp. observed on roll smears when analyzed statistically. However, OTOMAX has shown only moderate efficacy towards some gram positive cocci, including some *staphylococcus*species. There were no other statistical differences between Otomax®; and Panolog with respect to efficacy against bacteria.

This study showed OTOMAX to be both safe and effective for the treatment of otitis externa in dogs.

10. Adverse Reactions:

A total of 13 cases of 341 dispensed test articles (both OTOMAX and Panolog Ointment) exhibited adverse reactions (8 for OTOMAX; 5 for Panolog Ointment). Adverse reactions included redness of pinna and skin(1), redness and bumps on pinna (1), scratching and snorting(1), discomfort during

cleaning or medication(5) for OTOMAX. Panolog Ointment adverse reactions included head shaking(1), vomiting after three days of treatment(1), redness and swelling(1), difficulty in medicating(1) and increased scratching(1).

Overall, there were few adverse reactions for either treatment. OTOMAX and Panolog Ointment were considered equivalent in this study, with regard to safety.

D. Therapeutic Equivalence Study (C-5-87)

Name and Address of Investigator:

A.M. Benitz, D.V.M.
Schering Animal Health
P.O. Box 608
Allentown, N.J . 08501

General Design of the Investigation:

1. Purpose:

   Early efficacy studies were discontinued because the performance of the product was in question. Subsequently, the excipients were changed, and it was proposed that a formulation change would increase the shelf life stability of the active ingredients.

   The purpose of this study was to determine if differences in excipients between OTOMAX and Topagen Ointment would affect the efficacy of the active ingredients.

2. Test Animals:

   Species: Canine, beagle
   Number of Animals: 21
   Age Range: Young adult or adult
   Weight Range: 15-30 lbs.
   Sex: Mixed
   Acclimation: 2 weeks
   Supplier: Schering Toxicology, Lafayette, N.J.
   Diet: Purina 5006, water *ad libitum*

3. Test Articles:

   1. TOPAGEN Ointment: Gentamicin 3.0 mg/g and betamethasone 1.0 mg/g
   2. TOPAGEN Mineral Oil: Gentamicin 3.0 mg/g and betamethasone 1.0 mg/g
   3. Placebo: Mineral Oil formulation without active ingredients.

4. Treatment Schedule:

   Bacterial otitis externa was induced in twenty-one dogs using *S. aureus* and were randomly assigned into 3 treatment groups. After infection and assignment of groups treatments commenced. Treatments were given according to label instructions for TOPAGEN Ointment.

   Blinding was accomplished by coding each formulation. The code was broken at the conclusion of the trial.

5. Study Duration:

   11 days

6. Parameters Measured:

   Clinical
   1. Discomfort
   2. Inflammation
   3. Swelling
   4. Exudates - odor, color, quantity

   Microbiological
   Agar plates containing selective media for bacteria or fungi were inoculated with ear swabs collected at each evaluation point from each dog. Resulting growth was scored according to the amount of bacteria and/or *M. pachydermatis present*.

7. Summary of Results:

   TOPAGEN and TOPAGEN Mineral Oil adequately controlled clinical signs associated with the induced otitis externa and effectively eliminated the bacterial infection. Topagen and Topagen Mineral Oil were not statistically different from each other but were statistically superior to placebo.

8. Statistical Analysis:

   The variables discomfort, swelling and odor were analyzed by Fisher's Exact Test. The variables inflammation and quantity of exudate were analyzed by Ridit Analysis. Ridit analysis was used to analyze the culture scores for each selective medium. All of the above was performed separately for each observation day.

   For the clinical observations, no significant differences between groups were observed on day 1, indicating comparable infections in all three groups. At the majority of the later dates, the TOPAGEN Mineral Oil group was significantly better than the Placebo group, and not significantly different than the TOPAGEN group.

   For the microbiology culture observations, all groups were comparable on day 0 and day 1. No differences between the TOPAGEN Mineral Oil group and the TOPAGEN group were detected on any of the four media.

9. Conclusion:

   TOPAGEN and TOPAGEN Mineral Oil were both effective in controlling the clinical signs associated with an induced bacterial otitis externa as well as eliminating the associated bacterial infection. There was no significant difference in either clinical or bacteriological parameters between the TOPAGEN and TOPAGEN Mineral Oil formulations. Treatment with TOPAGEN and TOPAGEN Mineral Oil was both safe and effective.

10. Adverse Effects:

    No adverse effects were observed during this trial in any animal receiving TOPAGEN, TOPAGEN Mineral Oil or Placebo.

Corroborative Efficacy Study
Data from thirty-six dogs initially presented for enrollment in the Positive Controlled Clinical Evaluation study (V87-008), but who failed to meet specific entrance requirements were analyzed separately to support the efficacy of OTOMAX against *Malassezia*spp. Refer to page 6 of this Freedom of Information summary for information on the parent study. These cases had a *Malassezia*spp. infection and no bacterial infection, as confirmed by roll smear. Evaluation of the thirty-six cases indicated that OTOMAX and Panolog were equivalent in reducing *Malassezia*spp. and controlling clinical signs.

III. TARGET ANIMAL SAFETY

A. Target Species Final Safety Study (C-4-85)

Names and Addresses of Investigators:

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General Design of the Investigation:

1. Purpose:

   To determine the safety of OTOMAX when 4 (1X), 12 (3X) or 20 (5X) drops are administered into the ear canals of dogs twice a day for 21 consecutive days.

2. Test Animals:

   Six male and six female dogs, 6.5-11.4 kg in weight, were used in this study. Two males and two females were randomly assigned to each group.

3. Control Animals:

   Two male and two female dogs, 8.6-10.7 kg in weight, received 20 drops of placebo per ear twice a day for 21 days. Four additional dogs (two of each sex), 7.9-11.6 kg in weight, served as untreated controls.

4. Ear Condition:

   Two days prior to the initiation of treatment, all dogs were anesthetized and the right ears were lightly cauterized and infected with a broth culture of *Staphylococcus aureus*.

5. Dosage Form:

   OTOMAX was received as an opaque ointment in metal squeeze tubes. Placebo was packaged identically but labelled as such and contained no active ingredients.

6. Route of Administration:

   Otically, into the ear canal.

7. Dosages Used:

   The recommended dose for this product is 4 drops twice a day for 7 days for dogs weighing 30 lbs. or less. As all dogs on study were under this weight limit, 4, 12 or 20 drops of OTOMAX were administered twice a day for 21 consecutive days.

8. Test Duration:

   32 days

9. Parameters Measured:

   Clinical Observations
   1. Temperature
   2. Pulse
   3. Respiration
   4. Food Consumption
   5. Ear Evaluation Scores
   6. Behavior/Attitude/Appearance

Hematology
1. RBC
2. Total WBC
3. Differential WBC
4. Packed Cell Volume
5. Hemoglobin
6. MCV
7. MCH
8. MCHC

Serum Chemistry
1. SGOT
2. SGPT
3. GGT
4. LDH
5. Alkaline Phosphatase
6. Total Bilirubin
7. Direct Bilirubin
8. Creatinine
9. BUN
10. BUN/Creatinine Ratio
11. Glucose
12. Cholesterol
13. Albumin
14. Globulin;
15. Albumin/Globulin Ratio
16. Total Protein
17. Phosphate
18. Calcium
19. Chloride
20. Potassium
21. Sodium

Urinalysis
1. Appearance
2. pH
3. Specific Gravity
4. Ketones
5. Protein
6. Glucose
7. Blood
8. Leukocyte Esterase

Urine Sediment
1. Cells
2. Crystals
3. Bacteria
4. Casts
5. M. pachydermatis

Fecal Blood
1. Frank
2. Occult

Body Weights
1. Initial
2. Weekly
3. Terminal

10. Results

a. Overt Toxicity

Elevated rectal temperatures (equal to or greater than 103 degrees F) were seen in all groups (except 1X) prior to treatment and early in therapy. Infection of the penile sheath (as indicated by a purulent discharge) was seen with similar frequency in all groups. Difficulties in catheterization were experienced with 1X males. Ocular discharge was limited to the placebo and 3X groups. Untreated controls and placebo-treated dogs had higher edema scores. Emesis was seen only in 5X dogs after 5-6 days of treatment.

b. Hematology

A generalized leukocytosis (range of means from 20.4 thousand/cmm in the 1X group to 24.8 thousand/cmm in the 3X group) was seen in all groups prior to treatment but post induction of infection. Periodic elevations in band cells were seen in all groups with the highest peaks noted in animals in the 3X and 5X groups.

c. Serum Chemistry

Frequent sporadic elevations in GGT ranging from 9 to 30 units/L (normal is less than 8 units/L) were noted in all groups pre and post treatment. There were generalized increases in albumin values post treatment for the (1X, 3X, and 5X), although the values remained within the normal range. There were sporadic increases in alkaline phosphatase values up to 64 IU/L (placebo and 5X). However, all values had returned to the normal range by the end of the study. Elevations of Lactate Dehydrogenase (LDH) up to 429 IU/L (normal was less than 293 IU/L) were noted post infection. Increased values (up to 845 IU/L) persisted in all groups throughout the study, although values had returned to the normal range at the study conclusion. The 1 X group consistently had the highest values (6 of 12 sample means were above the normal range). There were isolated incidents of potassium values above normal (5.5-6.1 mmol/L), but the means were within the normal range. There were generalized increases in triglyceride levels in the placebo, 1X, 3X, and 5X groups. The untreated control group did not show such a trend towards increasing values. All mean triglyceride values were within the normal range.

d. Urinalysis

Composite urinalysis results were within the normal range. There were rare isolated incidents of findings outside the normal range, including hematuria (2+ Red blood cells), which could be attributed to catheterization.

e. Urine Sediment

No trends were noted. The sediment results were within the normal range, with the exception of isolated incidents of elevated red blood cells (30-70/HPF) and elevated white blood cells (10-30/HPF).

f. Fecal Blood

Occult blood was a frequent finding in all treatment groups.

g. Body Weight

All animals in the study maintained their weight.

h. Statistical Analysis:

Parameters were evaluated for biological and toxicological rather than statistical significance.

11. Conclusions

Most overt and all hematological changes appeared to be directly or indirectly related to the infection model used. Variations in serum chemistry were either within normal range or isolated incidents. All values were within the normal range at the conclusion of the study. Therefore, none of these changes were considered to be toxicologically significant.

Treatment related changes were limited to a lower edema score in treated vs. untreated control and placebo groups and emesis at 5X after 5-6 days of treatment. Both are typical responses to steroid therapy.

In conclusion, OTOMAX administered otically, even at 1, 3, and 5X doses and for prolonged therapy, is well tolerated by the target species.

IV. HUMAN FOOD SAFETY

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 in dogs, which are non-food animals.

Human Safety Relative to Possession, Handling, and Administration:
There is a bolded statement on the front panel of all labeling components "Keep out of reach of children."

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of section 512 of the Act and section 514.111 of the regulations. It demonstrates that Otomax® (betamethasone valerate, gentamicin sulfate, and clotrimazole), when used under labelled conditions of use, is safe and effective.

This product qualifies for a period of three years of marketing exclusivity under section 512 (c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

Betamethasone, gentamicin, and clotrimazole are previously approved drugs for use in dogs. This NADA provides for a two-way combination (betamethasone/gentamicin and clotrimazole) of the approved drugs. It qualifies for a three year period of marketing exclusivity because new clinical and field investigations were required for approval of this drug in combination and were conducted or sponsored by the applicant.

This drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of and microbiological components of otitis externa. Additionally, veterinary expertise is needed to ensure that the tympanic membrane is intact prior to initial administration of the drug.

GUIDELINE FOR DRUG COMBINATIONS FOR USE IN ANIMALS
Each of the drug components in this combination is approved individually. One approved two-way combination consists of betamethasone and gentamicin, Topagen® Ointment. The other component, clotrimazole, is approved for use in the treatment of yeast infections in humans. It is also approved as Veltrim® for topical use in the treatment of the fungal infections caused by *Microsporum canis*and *Trichophyton mentagrophytes*in dogs and cats. Safety and efficacy information is available on each component of this combination. The Guideline for Drug Combinations is generally applied to new drug combinations. The Guideline states that the combination of the drugs provides a benefit that cannot be obtained by the use of each of the drugs individually (i.e., each drug has made a contribution). A 2-way combination must be better than each of the components. It is prudent to state that the effect of betamethasone will mitigate clinical signs of inflammation both singularly and in combination with no antibacterial or antifungal effect. This New Animal Drug Application satisfies the drug combination policy because the sponsor has provided evidence that the combination product is superior to each component (gentamicin/betamethasone and clotrimazole) of the combination. The betamethasone reduces clinical signs of inflammation; the gentamicin reduces susceptible bacterial growth, and clotrimazole reduces *Malassezia*spp. growth. Both bacteria and *Malassezia*spp. can be components of otitis externa in the dog.

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.