FREEDOM OF INFORMATION SUMMARY

NADA 141-177

MOMETAMAX™ Otic Suspension for Dogs

(gentamicin sulfate, mometasone furoate monohydrate, clotrimazole)

For use in the treatment of otitis externa associated with yeast (*Malassezia pachydermatis*) and/or bacteria susceptible to gentamicin in dogs.

Sponsored by:

SCHERING-PLOUGH ANIMAL HEALTH

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FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

NADA Number: 141-177

Sponsor: Schering-Plough Animal Health Corporation
1095 Morris Ave.
Union, N. J. 07083

Established Name: Gentamicin sulfate, Clotrimazole, Mometasone furoate monohydrate

Trade Name: Mometamax™ Otic Suspension

Marketing Status: This is a prescription product that includes the caution statement as follows: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

II. INDICATIONS FOR USE:

Mometamax™ Otic Suspension is indicated for the treatment of otitis externa associated with yeast (*Malassezia pachydermatis*) and/or bacteria susceptible to gentamicin in dogs.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE:

A. Dosage Form:

Mometamax™ is a white, opaque otic suspension. The final dosage form consists of 0.3% Gentamicin Sulfate, 0.1% Mometasone furoate monohydrate, 1.0% Clotrimazole, Plasticized Hydrocarbon Gel Base and Mineral Oil USP. It is available in 15g, 30g, and 215g plastic dispensing bottles, each with attachable applicator tip for otic use.

B. Route of Administration:

Mometamax™ should be administered aurally. The external ear canal should be thoroughly cleaned and dried before treatment.

C. Approved Dose:

Verify that the eardrum is intact. For dogs weighing less than 30 lbs, instill 4 drops from the 15g or 30g bottle (2 drops from the 215g bottle) of MOMETAMAX™ Otic Suspension twice daily into the ear canal. For dogs weighing 30 lbs. or more, instill 8 drops from the 15g or 30 g bottle (4 drops from the 215g bottle) twice daily into the ear canal. Therapy should continue for 7 consecutive days.

IV. EFFECTIVENESS:

A. Dose Selection/Rationale:

The rationale for development of this product was to provide the veterinary practitioner with a broader range of otic products while offering a new otic which combines effectiveness against otitis externa with an alternate anti-inflammatory component. Mometamax™ is identical to the currently approved Schering-Plough product, Otomax® Ointment (NADA 140-896), with the exception of the substitution of 1 mg/g mometasone furoate monohydrate (in Mometamax™) for 1 mg/g betamethasone valerate (in Otomax®). The antifungal and antibacterial data used to support the effectiveness of Otomax® were applied to Mometamax™ since the active ingredients against fungi and bacteria are unchanged. Because the only change was the one-to-one substitution of the anti-inflammatory agents, the dose selected for clinical trials for Mometamax™ was the same as for Otomax®.

In the screening that led to the identification and selection of mometasone furoate monohydrate, it was found that furoates, especially in the 17 position, exhibit high topical potency with little systemic effect. The percutaneous absorption and excretion of mometasone ointment at 1 mg/g was evaluated after single topical applications of radiolabelled ointment to rats, rabbits and dogs with intact skin. In all three species, systemic absorption was found to be minimal and ranged from 2% in dogs to 6% in rabbits over a 5-7 day period. Mometasone furoate at a concentration of 1 mg/g is currently available as the human product, Elocon® Cream.

B. Field Investigations:

"Comparison of Two Otic Formulations in Dogs: Otomax® Ointment vs. Gentamicin-Mometasone-Clotrimazole (SCH 480) Ointment" (Study V95-271)

1 Investigators:

The following investigators produced a sufficient number of cases to be included in the safety and effectiveness analysis:

Dr. R. W. Cannon Small Animal Hospital 4314 Main Street Kansas City, MO 64111	Dr. Donald Copeland Bellaire Richmond Pet Hospital 5808 Bissonnet Houston, TX 77081-6599
Dr. L. D. Eckermann Westbury Animal Hospital 4917 South Willow Drive Houston, TX 77035	Dr. Ben Garrett 1846 South Oates Dothan, AL 36301
Dr. Richard W. Green Capitol Plaza Veterinary Clinic 2200 East South Boulevard Montgomery, AL 36116	Dr. Terry Grieshaber Animal Allergy & Skin Disease Center 6327 North Keystone Indianapolis, IN 46220
Dr. K. Scott Griffin Carriage Hills Animal Clinic 3200 Eastern Bypass Montgomery, AL 36116	Dr. Andrew Pickering Wabash Valley animal Hospital 3004 South 7th Street Terre Haute, IN 47802
Dr. Tod Schadler 2685 South High Street Columbus, OH 43207	Dr. Roger Sifferman Bradford Park Veterinary Hospital 1255 East Independence Springfield, MO 65804
Dr. Jack W. Whitmore Stuebner Airline/Champions Veterinary Hospital 16116 Stuebner Airline Spring, TX 77379	Dr. Ken D. Winters 7280 W. 105th Street Overland Park, KS 66212 3910 W. 95th Street Prairie Village, KS 66207
Dr. Robert Yelland Lewelling Veterinary Clinic 525 Lewelling Boulevard San Leandro, CA 94579	

2. General Design of the Investigation:

Purpose:

To compare the safety and effectiveness of a clotrimazole-gentamicin mometasone (Mometamax™) combination otic product with a FDA-approved product with similar claims (Otomax®), under clinical conditions of use against concurrent bacterial and yeast (*Malassezia pachydermatis*) infections.

Test Animals:

Species: Canine, multiple breeds
Number of Subjects: 141 treated with Mometamax™ and 146 treated with the control drug, Otomax® were evaluated for safety. Of these cases, 117 dogs treated with Mometamax™ and 123 dogs treated with Otomax® were included in the evaluation for effectiveness.
Age Range: 2 months -16.4 years
Weight Range: 5 lbs.-138.0 lbs.
Sex: 79 females and 68 males were treated with Mometamax™ and 77 females and 73 males were treated with Otomax®.

Test Articles:

Mometamax™ Otic Suspension: 10 mg/g clotrimazole, 1.0 mg/g mometasone furoate monohydrate, and 3.0 mg/g gentamicin sulfate.

CONTROL: Otomax® Ointment: 10 mg/g clotrimazole, 1.0 mg/g betamethasone valerate, and 3.0 mg/g gentamicin sulfate.

Treatment Schedule

Dosage Groups: Group T1 and T3 – Otomax®
Group T2 and T4 – Mometamax™

Dosage: <30 lbs - 4 drops per affected ear or
>30 lbs - 8 drops per affected ear

Route of Administration: Otic

Frequency of Treatment: Twice a day for 7 days.

Duration of Study: Animals were treated for 7 days with either Otomax® or Mometamax™ and returned for reevaluation 2 - 8 days after treatment was completed.

Inclusion Criteria: Dogs must have concurrent bacterial and *Malassezia pachydermatis* infections in either one ear or both ears as determined by an ear swab. If both ears were infected, only the right ear was evaluated. Dogs with ear mite infestations were excluded as well as those receiving concomitant local or systemic antibiotic, anti-inflammatory or antifungal therapy.

Parameters measured: A complete physical and otoscopic examination was made of both ears. The ears were cleaned with an ear cleansing solution free of antimicrobial and anti-inflammatory activity. Discomfort, pinna erythema, ear canal erythema, ear canal swelling and exudate (presence, quantity, type and odor) were evaluated prior to treatment and 8-10 days after completion of treatment. A quality of improvement survey was completed by the investigator and the owner at the second evaluation.

Pivotal Effectiveness Variables:

- Discomfort (mild/moderate, marked)
- Pinna erythema (mild/moderate, marked)
- Ear canal erythema (mild/moderate, marked)
- Ear canal swelling (mild/moderate, marked)
- Exudate - presence
  quantity (mild/moderate, marked)
  type (waxy, coffee ground or purulent),
  odor (mild/moderate, marked)
- Owner final evaluation
- Investigator final evaluation

3. Results:

Discomfort: Discomfort was similarly alleviated by both treatments. At the final evaluation: 81% (100/123) and 89% (104/117) of the dogs in Otomax® and Mometamax™, respectively, showed no sign of discomfort.

Pinna Erythema: Upon final evaluation of pinna erythema, 86% of the Otomax® treated animals and 90% of the Mometamax™ treated animals had no sign of pinna erythema.

Ear Canal Erythema: Upon final evaluation of canal erythema, 73% of the Otomax® treated animals and 75% of the Mometamax™ treated animals had no sign of canal erythema.

Ear Canal Swelling: Upon final evaluation of canal swelling, 89% of the Otomax® treated animals and 92% of the Mometamax™ treated animals had no sign of canal swelling.

Exudate: More dogs treated with Otomax® did not have exudate present at the end of the study compared with dogs treated with Mometamax™ (72% versus 62% respectively). Twenty-seven percent (27%) of dogs treated with Otomax® had mild/moderate discharge at the end of the study compared to 38% of dogs treated with Mometamax™. Both treatments were similar in reducing purulent discharge. Four percent (4%) of dogs treated with Otomax® had purulent discharge after completing treatment compared with 3% of Mometamax™ treated dogs. Twenty percent (20%) of dogs treated with Otomax® had waxy discharge present at the end of the study compared to 30% of Mometamax™ treated dogs. Dogs treated with either Otomax® or Mometamax™ were similar in reducing odor associated with otitis externa (89% for both treatment groups at the end of the study).

Owner and Investigator final evaluation: Both were similar for dogs treated with either Mometamax™ or Otomax®. Investigator overall evaluation rated Otomax® excellent or good in 92% of the cases compared to 91% of the Mometamax™ treated cases. Ninety-two percent (92%) of the dogs treated with Otomax® were rated overall excellent or good by owners compared to 95% of the dogs treated with Mometamax™.

4. Statistical Analysis:

A total of 240 (123 Otomax®, 117 Mometamax™) cases qualified for inclusion in the statistical analysis for effectiveness. A total of 287 (146 Otomax®, 141 Mometamax™) cases qualified for the safety evaluation. Data were pooled across the 13 investigators supplying qualified cases for effectiveness evaluation.

Because Otomax® was a positive control, the clinical responses of each treatment were evaluated utilizing confidence intervals. The confidence intervals were calculated by examining the improvement in clinical signs. The animals that showed improvement from Day 0 to Day 8 in the clinical score were classified as "improved". If the animals stayed the same or got worse, they were classified as "Stayed the same/Got worse". Any animal that was normal at both the start and end of the study for a certain variable was excluded from the analysis for that variable.

The percentage of animals showing improvement with Otomax® was subtracted from the percentage of animals showing improvement with Mometamax™ Otic Suspension. A 90% confidence interval was constructed around this difference. The lower bound of this interval represents the minimum predicted level of effectiveness of the test article compared to the positive control (i.e., at worst, the percent improvement with Mometamax™ Otic Suspension may be as much as x% less than the percent improvement with Otomax®). Most of the clinical signs showed a percent improvement in the 90-99% range (see Table 1). For this reason, a lower bound of –10% for the 90% confidence interval was used as the criterion for determining that Mometamax™ Otic Suspension was "no worse than", i.e. "at least as good as" Otomax®.

Using this definition, four parameters did not meet the criteria for classification of "no worse than" (Table 1). These parameters include presence of exudate, type of exudate, quantity of exudate, and canal erythema. Canal swelling, with a lower bound of –10.6% as the difference between Mometamax™ and Otomax®, was very close to the criterion boundary. The remaining five parameters, pinna erythema, level of discomfort, odor of exudate, investigator evaluation and owner evaluation satisfy the criteria and can be classified as "at least as good as" the positive control.

Table 1 Improvement in Clinical Variables

	Mometamax	Otomax	Mometamax - Otomax

Variable	% Improve-ment	% Improve-ment	Differ-ence	Lower 90% confidence bound	Upper 90% confidence bound
Discomfort	93.6% (n=110)[a]	88.7% (n=115)	4.9%	-3.0%	14.0%
Pinna Erythema	89.9% (n=69)	87.3% (n=71)	2.5%	-8.7%	15.8%
Canal Erythema	83.2% (n=113)	90.8% (n=120)	-7.6%	-14.9%	-0.4%
Canal Swelling	95.7% (n=94)	97.8% (n=90)	-2.0%	-10.6%	5.0%
Presence of Exudate	61.2% (n=71)	70.8% (n=120)	-9.6%	-20.9%	1.2%
Type of Exudate [b]	87.1% (n=31)	82.1% (n=28)	5.0%	-15.1%	28.4%
Quantity of Exudate	75.9% (n=116)	84.2% (n=120)	-8.3%	-18.7%	1.5%
Odor of Exudate	98.2% (n=109)	96.5% (n=115)	1.6%	-4.3%	8.7%
Investigator Evaluation	91.5% [c] (n=117)	91.9% [c] (n=123)	-0.4%	-8.9%	7.3%
Owner Evaluation	94.9% [c] (n=117)	91.8% [c] (n=122)	3.1%	-4.0%	11.3%

Notes:
[a] The number of animals in this group on which the percentage is based. The animals that were normal on both Day 0 and Day 8 were excluded.
[b] Animals that had either none, waxy, or coffee grounds type of exudate on Day 0 and either none, waxy or coffee grounds type of exudate on Day 8 were excluded.
[c] Percent of animals that are either "Excellent" or "Good".

Time is a factor in the resolution of exudate; it can take more than 8-10 days for exudate to decrease by significant levels. Therefore, if we examine marked exudate, which is the extreme end of the quantity of exudate, and improvement from marked exudate, Mometamax™ Otic Suspension and Otomax® were similar in this parameter. This parameter satisfies the criteria and can be classified as "at least as good as".

Therefore, overall Mometamax™ Otic Suspension meets the criteria that it is at least as good as Otomax®.

5. Adverse Effects:

Nine dogs out of 287 cases (both Mometamax™ and Otomax®) exhibited adverse reactions (6 dogs treated with Otomax® and 3 dogs treated with Mometamax™).

Adverse reactions reported in dogs treated with Mometamax™ included: bilateral hyperemia of pinna (1 dog), vomition during treatment (1 dog), and diarrhea (1 dog). Adverse reactions reported in dogs treated with Otomax® included: inflammation of pinna (1 dog), external ear canal inflammation (1 dog), diarrhea followed by constipation (1 dog), ataxia (1 dog), increased reluctance to accept treatment (1 dog), and deafness (1 dog). All 9 adverse reactions reverted to normal following cessation of treatment.

6. Conclusion:

This controlled clinical study demonstrated that Mometamax™, a combination otic product, administered as recommended was both safe and effective for the treatment of otitis externa in dogs.

V. ANIMAL SAFETY:

Target Animal Safety information for topical application of gentamicin sulfate and clotrimazole for the treatment of otitis externa in dogs is incorporated by reference to the original new animal drug application (NADA) for the otic product, Otomax® (NADA 140-896) which was approved on June 9, 1993.

A. Six-Month Dermal Toxicity Study of SCH 32088 (Mometasone furoate Ointment) 0.1% in Dogs with Intact Skin:

1. Purpose: To assess the dermal irritation and systemic toxicity of SCH 32088 (mometasone furoate) 0.1% after daily topical application to Beagle dogs with intact skin for six months.

2. Study Director: Robert E. Squibb, Ph.D.
Department of Pathology and Toxicology
Pharmaceutical Research Division
Schering Corporation
Lafayette, N. J. 07848

3. General Design:

Animals: 20 male and 20 female Beagle dogs approximately 11 months of age at the onset of the study. Body weight ranged from 6.4 to 11.8 kg. Dogs were randomly assigned to five groups (4/sex/group).

Dosage Form: Mometasone furoate 0.1% topical ointment.

Dosages:

Mometasone furoate 0.1%, 0.5 g/kg (12.5 X)
Mometasone furoate 0.1%, 1 g/kg (25 X)
Mometasone furoate 0.1%, 2 g/kg (50X)
Vehicle ointment, 2 g/kg
Untreated control, 0 g/kg

Route of Administration: Topical: Prior to dosing, and as needed throughout the study, each dog was prepared by clipping the skin of the flank and back free of hair. Medicated ointment or vehicle was applied daily to an area of skin comprising approximately 10% of the total body surface.

Study Duration: Daily application for six (6) months.

Pertinent Measurements/Observations: Dermal irritation, changes in physical appearance and behavior, physical examinations (including body temperature, respiratory and heart rates, blood pressure, electrocardiography), ophthalmic examinations, body weight, food consumption, hematological and blood chemistry data, gross and histological examination of selected organs at necropsy.

4. Results:

General Condition: Beginning at week 5, signs of muscle wasting were observed in one vehicle, two 1 g/kg and three 2 g/kg-dosed dogs. At the end of the study, two vehicle, three 0.5 g/kg, three 1 g/kg and four 2 g/kg-dosed dogs showed muscle wasting.

Physical Examination Data: No compound-related changes occurred in any of the groups during the course of the study.

Ophthalmology Data: No compound-related ocular changes occurred in any of the groups during the course of the study.

Dermal Response Data: Transient erythema was seen in 1/8 of the vehicle, 1/8 of the 0.5 g/kg, 2/8 of the 1 g/kg and 4/8 of the 2 g/kg-dosed animals. No edema was observed. Papules and/or pustules were common in all medicated groups and occasionally seen in the vehicle-treated group. Desquamation was occasionally

seen in all medicated groups. Less than normal hair growth was seen at the application site in all medicated groups by week 9. One dog in the 2 g/kg group presented with a 12 cm circular band of reddish skin on its midback during week 14. The lesion disappeared by week 17. Some dogs from all three medicated groups presented with bluish discoloration between weeks 17 and 21. These areas eventually, paradoxically, resulted in new hair growth.

Body Weight & Food Consumption: All untreated dogs gained weight. Body weight changes among the medicated groups were variable (some animals gained slightly while others lost slightly). Food consumption was normal for all animals.

Hematology: Minimal to moderate decreases in absolute lymphocyte counts were observed for most animals in all three medicated groups. Two males in the 2 g/kg group experienced mild increases in neutrophil counts at weeks 5 and 25. No consistent compound-related changes were observed in red cell parameters.

Clinical Chemistry: Transient, slight increases in cholesterol, and triglycerides were observed in medicated and vehicle-dosed groups. Lipemia was only at the week 5 interval in 1/8 vehicle-treated animals and in some animals from the 0.5 g/kg and 2 g/kg medicated groups.

Urinalysis: Slight increases in 24-hour urine volume were noted at weeks 13 and 25 in all three medicated groups.

Gross Pathology: At necropsy, muscle wasting with a generalized absence of fat was evident in selected animals from all medicated and vehicle-treated groups. Adrenal glands and uteri in selected animals from the 1 g/kg and 2 g/kg groups were smaller than respective organs in most control dogs. Hepatic enlargement and/or discoloration were noted in one 0.5 g/kg-dosed female, one 1 g/kg-dosed male and in six 2 g/kg-dosed animals. The thymus appeared fatty in most animals from the 2 g/kg group. Skin thickness appeared less at the application site for medicated dogs in comparison to untreated and vehicle-dosed dogs. Skin thinning also occurred at the non-dosed areas for medicated dogs and indicated systemic absorption of the drug substance. Additional skin changes included tufts of coarse brown or black hairs and/or multiple white scars in the neck and/or lumbar regions of selected animals from the medicated groups.

Microscopic Pathology: Compound-related changes in the skin of medicated animals included minimal or slight atrophy of the epidermis, hair follicles and adnexa in five to six animals from each group. Thinning of the stratum corneum was noted in most animals including controls. All males and four females (2 animals from the 1 g/kg and two from the 2 g/kg groups) had some degree of adrenal cortical atrophy with the zona fasciculata being the most affected. Centrilobular hepatocytomegaly was evident in one male dog from each of the three medicated groups. The majority of medicated males and selected medicated and vehicle-treated females exhibited fatty replacement of the bone marrow. Several males in all three medicated groups and all females in the 2 g/kg group had varying degrees of thymic involution. One male from the 2 g/kg group exhibited stomach mucosal erosion.

5. Conclusion:

Mometasone furoate ointment (0.1%) applied topically once daily to Beagle dogs for six months at approximately 12.5, 25 and 50 times the recommended label dose produced adverse effects typical of corticosteroid therapy. The doses administered in this study far exceed the recommended otic dose. For the labeled conditions of use, mometasone is safe for use on dogs in a 0.1 % formulation. Higher doses or prolonged use may result in clinical signs typical of corticosteroid therapy.

VI. HUMAN 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 drug is to be labeled for use 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 the labeling components “Keep this and all drugs out of the reach of children.”

VII. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that Mometamax™ Otic Suspension for dogs, when used under labeled conditions of use, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine the presence of otitis externa and the presence of bacterial and/or yeast and to monitor the safe use of the product.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

VIII. LABELING (Attached):

A. Package Insert
B. Bottle label (15g, 30g and 215g)