Approval Date: January 9, 2003

FREEDOM OF INFORMATION SUMMARY

NADA 141-177

MOMETAMAX™ Otic Suspension for Dogs

(gentamicin sulfate, mometasone furoate monohydrate, clotrimazole)

For the treatment of otitis externa in dogs caused by susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Pseudomonas spp*. [including *P. aeruginosa*], coagulase positive staphylococci, *Enterococcus faecalis, Proteus mirabilis* and beta hemolytic streptococci)

Sponsored by:

SCHERING-PLOUGH ANIMAL HEALTH

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FREEDOM OF INFORMATION SUMMARY

1. BACKGROUND INFORMATION:

a.	*File Number:*	NADA 141-177
b.	*Sponsor:*	Schering-Plough Animal Health Corporation 1095 Morris Avenue Union, NJ 07083 Drug Labeler Code: 000061
c.	*Established Name:*	Gentamicin sulfate, USP; mometasone furoate monohydrate; and clotrimazole, USP suspension
d.	*Proprietary Name:*	Mometamax ™ Otic Suspension
e.	*Dosage Form:*	Otic Suspension
f.	*How Supplied:*	15g, 30g, and 215g plastic bottles
g.	*How Dispensed:*	Rx
h.	*Amount of Active Ingredients:*	Each gram contains 3-mg gentamicin, 1-mg mometasone, and 10-mg clotrimazole.
i.	*Route of Administration:*	Otic
j.	*Species/Class:*	Dogs
k.	*Recommended Dosage:*	For dogs weighing less than 30 lbs, instill 4 drops from the 15-g and 30-g bottle into the ear canal (2 drops from the 215-g bottle) or, for dogs weighing 30 lbs or more, instill 8 drops from the 15- or 30-g bottle into the ear canal (4 drops from the 215-g bottle), once daily for 7 days.
l.	*Pharmacological Category:*	Gentamicin - aminoglycoside antibiotic Mometasone - synthetic adrenocorticoid Clotrimazole - imidazole antifungal agent

m. *Indications:*	MOMETAMAX™ Otic Suspension is indicated for the treatment of otitis externa in dogs caused by susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Pseudomonas spp*. [including *P. aeruginosa*], coagulase positive staphylococci, *Enterococcus faecalis, Proteus mirabilis* and beta hemolytic streptococci).
n. *Effect of Supplement:*	This supplemental approval adds the additional dosing frequency of once daily administration.

II. EFFECTIVENESS:

A. Dosage Characterization:

An original new animal drug application for Mometamax™ Otic Suspension for Dogs (NADA 141-177) was approved on December 5, 2000. The studies demonstrating the effectiveness of Mometamax™ administered twice daily are summarized in the original NADA 141-177 Freedom of Information Summary. This NADA 141-177 supplement is supported by data from one field study to confirm the effectiveness of Mometamax™ administered once daily for 7 days.

B. Field Study:

A Negatively Controlled Study to Assess the Field Effectiveness and Safety of Mometamax (SCH 480) Otic Suspension administered once daily (Study C00-055-00).

Investigators:

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

Dr. Greg Tremoglie Glenmoore Veterinary Hospital 3 Andover Rd. Glenmoore, PA 19343	Dr. Charles Schwirck Hillsborough Veterinary Hospital 210 Route 206 South Somerville, NJ 08876
Dr. Dave Lukof Harleysville Veterinary Hospital 391 Main St. Harleysville, PA 19438	Dr. Roger Sifferman Bradford Park Veterinary Hospital 1255 East Independence Springfield, MO 65804

Dr. Karen Oberhansley Whitehouse Veterinary Hospital P. O. Box 293 358 Main St. Whitehouse Station, NJ 08889	Dr. Dean J. Rund Grant Avenue Pet Hospital 1037 S. Grant Avenue Springfield, MO 65807
Dr. Robert Yelland VCA Lewelling Veterinary Clinic 525 Lewelling Boulevard San Leandro, CA 94579	Dr. Richard Benjamin Berkeley Dog & Cat Hospital 2126 Haste Street Berkeley, CA 94704

General Design of the Investigation:

Purpose: To compare the safety and effectiveness of a clotrimazole-gentamicin-mometasone (Mometamax™) combination otic product, administered once daily, to that of an excipient negative control, administered once daily, under clinical conditions of use against concurrent bacterial and yeast (*Malassezia pachydermatis*) infections.

Species: Canine, multiple breeds

Number of Subjects: 47 treated with Mometamax™ and 48 treated with excipient base (mineral oil in a plasticized hydrocarbon gel) were included for assessment of safety. Of these cases, 39 dogs treated with Mometamax™ and 36 treated with excipient base were included in the evaluation for effectiveness.

Age Range: 5 months -16 years

Weight Range: 5 lbs.-168 lbs.

Sex: 28 females and 19 males were treated with Mometamax™ and 24 females and 24 males were treated with excipient base.

Test Articles:

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

Negative Control: same excipient base found in Mometamax™, mineral oil-based system containing a plasticized hydrocarbon gel.

Dosage Groups:

Mometamax™ Otic Suspension

Negative Control (Excipient base)

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

Route of Administration: Otic

Frequency of Treatment: Once a day for 7 days.

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

Inclusion Criteria: Dogs had concurrent bacterial and *Malassezia pachydermatis* infections in either one ear or both ears as determined by an ear swab. The otitis externa was of sufficient severity that the sum of the clinical scores (graded on a scale of 0-3) associated with discomfort, ear canal erythema, ear canal swelling and exudate quantity was greater than or equal to 5. If both ears were infected, only the right ear was evaluated. Dogs had none of the exclusion criteria present, including otic foreign bodies, concurrent medications that could confound the study (i.e. otic preparations, systemic corticosteroids, antibiotic or antifungal therapy), occlusive masses, ruptured tympanic membranes, staff-owned pet, or pets enrolled in other field studies.

Parameters measured: A complete physical (including a hearing [clap] test) and otoscopic examination was performed on both ears. The ears were cleaned with an ear cleansing solution free of antimicrobial and anti-inflammatory activity. Discomfort, ear canal erythema, and ear canal swelling were considered the primary variables. Secondary variables included: odor, pinna erythema, exudate type, exudate quantity, and investigator and owner evaluations. All variables were evaluated prior to treatment and 2-7 days after completion of treatment.

Primary Effectiveness Variables:

- Discomfort (none, mild, moderate, marked)
- Ear canal erythema (none/normal, mild, moderate, marked)
- Ear canal swelling (none/normal, mild, moderate, marked)

Results:

Discomfort:

Upon final evaluation of discomfort: 74% (29/39) and 58% (21/36) of the dogs in Mometamax™ and placebo control groups, respectively, showed none to mild discomfort.

Ear Canal Erythema:

Upon final evaluation of ear canal erythema: 80% (31/39) and 50% (18/36) of the dogs in Mometamax™ and placebo control groups, respectively, showed none to mild ear canal erythema.

Ear Canal Swelling:

Upon final evaluation of ear canal swelling: 82% (32/39) and 67% (26/36) of the dogs in Mometamax™ and placebo control groups, respectively, showed none to mild ear canal swelling.

Statistical Analysis:

For discomfort, canal erythema, canal swelling, pinna erythema, exudate odor and quantity of exudate, 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 primary variables, discomfort, canal erythema and canal swelling, were analyzed with an exact Mantel Haenszel analysis of 2x2 tables, stratified by site, to compare the percentage of animals showing improvement with Mometamax compared with the placebo.

The secondary variables were pooled across sites and analyzed with an exact test of the difference between two percentages. The percentage of improvement was analyzed for the variables pinna erythema, exudate odor, and quantity of exudate. For owner evaluation and investigator evaluation, the percentage of cases that were rated as either "excellent" or "good" was analyzed. For type of exudate, animals that had purulent exudate on day 0 and either none, waxy or serous exudate on day 8 were classified as "improved." Animals that had purulent exudate on day 8 were classified as "not improved." Animals that had either none, waxy or serous type of exudate on day 0 and either none, waxy or serous type of exudate on day 8 were excluded from the calculation of percent improvement.

Statistical significance was declared at $p \leq 0.05$. See Table 1 for the results.

Table 1 Improvement in Clinical Variables

	Mometamax	Placebo	p-value, Mometamax vs. Placebo
Primary clinical variables			
Discomfort	70.3% (n=37)[a]	41.7% (n=36)	p=0.0326
Canal Erythema	74.4% (n=39)	36.1% (n=36)	p=0.0016
Canal Swelling	71.4% (n=35)	48.5% (n=33)	p=0.0436
Secondary clinical variables			
Pinna Erythema	73.5% (n=34)	50.0% (n=34)	p=0.0701
Type of Exudate [b]	57.1% (n=7)	40.0% (n=5)	p=0.6595
Quantity of Exudate	61.5% (n=39)	52.8% (n=36)	p=0.4821
Odor of Exudate	72.2% (n=36)	21.9% (n=32)	p=0.0020
Investigator Evaluation [c]	61.5% (n=39)	19.4% (n=36)	p=0.0022
Owner Evaluation [c]	74.4% (n=39)	55.6% (n=36)	p=0.1108

[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 serous type of exudate on Day 0 and either none, waxy or serous type of exudate on Day 8 were excluded.
[c] Percent of animals that are either "Excellent" or "Good."

Adverse Reactions:

There were no adverse reactions reported during the study in either of the Mometamax™ or placebo control groups.

Conclusion:

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

III. ANIMAL SAFETY:

Target Animal Safety information for Mometamax™ Otic Suspension is incorporated by reference to the original new animal drug application (NADA 141-177), which was approved on December 5, 2000.

In a field study not used to support effectiveness due to problems with the study design, ataxia, proprioceptive deficits, and increased water consumption were observed in less than 1% of 117 dogs following once-daily treatment with Mometamax™ Otic Suspension. Treatment with the investigational drug could not be ruled out as contributing to these observations. The ataxia and proprioceptive deficits reported in one dog resulted in that dog's withdrawal from the study.

IV. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Keep this and all drugs out of the reach of children."

V. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that Mometamax™ Otic Suspension, 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)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the Mometamax™ once daily application for which this supplement is approved.

Schering Plough holds the following patents on mometasone: 5,502,222 (expires June 1, 2014), 5,616,742 (expires May 22, 2015), 5,750,745 (expires May 30, 2015), 5,886,200 (expires June 25, 2017), and 6,127,353 (expires October 3, 2017).

VI. LABELING (Attached):

A. Package Insert
B. Bottle Label (15g, 30g, 215g)
C. Carton Label (15g, 30g, 215g)