Date of Approval: April 29, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-600

Mometamax Single™

(gentamicin, posaconazole, and mometasone furoate otic suspension)

Dogs

Mometamax Single™ is indicated for the treatment of otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa*) in dogs.

Sponsored by:

Intervet, Inc.

Executive Summary

Mometamax Single™ (gentamicin, posaconazole, and mometasone furoate otic suspension) is approved for the treatment of otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa*) in dogs.

Mometamax Single™ is an otic suspension with three active ingredients: an antibacterial (gentamicin), antifungal (posaconazole), and anti-inflammatory (mometasone furoate). One dose should be administered once to each affected ear by a veterinary professional. The dog should be adequately restrained after administration to minimize head shaking. The external ear canal should be cleaned before administering the product, and then not cleaned for 33 days afterward.

Safety and Effectiveness
The sponsor conducted a field study in client-owned dogs of both sexes and a range of ages and weights. The dogs had intact tympanic membranes and were diagnosed with otitis externa based on the following four clinical signs: erythema, swelling, ulceration, and exudate. Each of the four clinical signs was scored from 0 (none) to 3 (severe), and dogs were required to have an overall clinical otitis score of at least 6 to be enrolled. Only one ear per dog was included in the effectiveness evaluation.

Before treatment was administered on Day 0, samples for bacterial and fungal culture were collected from the dogs' external ear canals and their affected ear or ears were cleaned with saline. After this initial cleaning, the ears were not cleaned or flushed again during the study. A veterinary professional administered either Mometamax Single™ or vehicle control to the dogs' affected ear or ears on Day 0. The vehicle control had the same formulation and inactive ingredients as Mometamax Single™ but did not include the active ingredients.

A dog was considered a treatment success if the overall clinical otitis score was ≤3 on Day 33 (±3) and no single clinical score for otitis externa worsened. Compared to dogs in the control group, more dogs in the treatment group were treatment successes (80.5% versus 19.6%). The culture results showed that Mometamax Single™ was successful at treating cases of otitis externa caused by *S. pseudintermedius*, *P. aeruginosa*, and *M. pachydermatis*. Adverse reactions in treated dogs included vomiting, decreased appetite, pruritus, ear pruritus, and disorientation.

The sponsor conducted an *in vitro* laboratory study that demonstrated that the presence of mometasone furoate does not interfere with the activity of the two microbiologically active ingredients, gentamicin and posaconazole, against bacterial and yeast isolates, respectively. The bacterial and yeast isolates that were tested in the study were selected from clinical cases of otitis externa in dogs. The minimum inhibitory concentrations indicated that gentamicin is active against *P. aeruginosa* and *S. pseudintermedius* and posaconazole is active against *M. pachydermatis*.

The sponsor also conducted a margin of safety laboratory study in healthy, intact male and female beagle puppies. The puppies were administered Mometamax Single™ in both ears on three dosing days, 14 days apart, at 0X, 1X, 3X, and 5X the label dose. All dogs remained healthy with normal hearing throughout the study. Aural administration of

Mometamax Single™ was associated with mild eosinopenia in the 3X and 5X groups and suppressed serum cortisol levels in all three treatment groups. Pathology findings included lower mean adrenal weights and mild atrophy of the adrenal cortex in dogs in the 3X and 5X groups. Histopathology findings included minimal to mild atrophy of the external ear canal epidermis and of the external surface of the tympanic membrane in all three treatment groups. The mild adrenal changes, mild thinning of the external ear canal and tympanic membrane, and mild suppression of the hypothalamic-pituitary-adrenal axis are consistent with systemic absorption of mometasone furoate as seen with the administration of exogenous corticosteroids.

User Safety
The labeling for Mometamax Single™ includes safety information for people who handle, administer, or are exposed to the drug. Dogs should be restrained after treatment to minimize head shaking to reduce potential splatter of the product and prevent accidental eye exposure in people and dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of Mometamax Single™, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-600

B. Sponsor

Intervet, Inc.
126 E Lincoln Ave.
Rahway, NJ 07065

Drug Labeler Code: 000061

C. Proprietary Name

Mometamax Single™

D. Drug Product Established Name

gentamicin, posaconazole, and mometasone furoate otic suspension

E. Pharmacological Category

Antibacterial, antifungal, and anti-inflammatory

F. Dosage Form

Otic suspension

G. Amount of Active Ingredient

A 0.8 mL dose delivers 6.88 mg gentamicin, 2.08 mg posaconazole, and 1.68 mg mometasone furoate.

H. How Supplied

Mometamax Single™ is supplied in a bottle containing 24 mL (20 doses) co-packaged with one plastic-wrapped dosing syringe with attached bottle adapter, and 19 additional dosing syringes.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Mometamax Single™ should be administered by veterinary personnel. The dose volume is 0.8 mL per affected ear. Verify the tympanic membrane is intact prior to administration.

K. Route of Administration

Otic

L. Species/Class

Dogs

M. Indication

Mometamax Single™ is indicated for the treatment of otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa*) in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

The dose of 0.8 mL administered to the external ear canal once was selected for the treatment of otitis externa based upon the following studies:

A pilot ear swab depletion study (S16198-00) utilizing a preliminary formulation and an ear swab depletion study (S16199-00) utilizing the final product formulation were conducted to characterize the depletion of gentamicin, posaconazole, and mometasone furoate from the external ear canal of healthy, normal ears in dogs following topical otic administration. In both studies, a 0.8 mL dose containing 6.88 mg of gentamicin, 2.08 mg of posaconazole, and 1.68 mg of mometasone furoate monohydrate was administered to each ear of healthy Beagle dogs on Day 0. Ear wax samples were collected from the dogs and analyzed for the presence of the active ingredients up to Day 14 (Study S16198-00) and up to Day 45 (Study S16199-00). Detectable levels of all 3 active ingredients depleted gradually over time, and regression analysis was performed to define the therapeutic concentration-time interval for the slowest-depleting active ingredient. The results were variable between the two studies for the slowest-depleting active ingredient, but Mometamax Single™ may remain above subtherapeutic levels for at least 30 days. Due to increased absorption through the disrupted skin barrier and drug degradation secondary to inflammation, drug depletion may occur faster when administered to dogs with otitis externa compared to dogs with healthy ears. For this reason, an adjustment was applied to the final day of evaluation in the pivotal effectiveness study (field study). The final day of evaluation in the field effectiveness study (S16068-00) was Day 33.

B. Substantial Evidence

1. Field Study

   Title: Evaluation of Safety and Efficacy of An Otic Suspension Containing Gentamicin, Mometasone Furoate, and Posaconazole for the Treatment of Otitis Externa in Client-Owned Dogs Under Field Conditions. (Study No. S16068-00)

   Study Dates: August 12, 2020 to September 5, 2024

Study Locations: Veterinary clinics in the United States from the following locations participated in the study:

Decatur, IL
Eden, NC
Kimberling City, MO
Liverpool, NY
Lumberton, TX
Marion, OH
Muncy, PA
New Port Richey, FL
Nixa, MO
Omaha, NE
Papillion, NE
Quakertown, PA
Springfield, MO
Sulfur, LA
Wichita Falls, TX
Wildwood, FL
Wilson, NC

Study Design:

Objective: The primary objective of this study was to evaluate the safety and efficacy of a novel otic suspension containing gentamicin, mometasone furoate, and posaconazole over a period of 33 days for the treatment of otitis externa in client-owned dogs under field conditions.

A secondary objective of this study was to assess the rapid onset of activity (clinical improvement within the first seven days after treatment) in treating otitis externa in a field setting.

Study Animals: Three hundred seventy-two (372) client-owned dogs were enrolled and included in the safety analysis. Two hundred forty-five (245) were administered Mometamax Single™ and 127 were administered the vehicle control. Two hundred fifty-four (254) dogs were included in the effectiveness analysis; 163 were administered Mometamax Single™ and 91 were administered the vehicle control. The dogs enrolled were 2.8 months to 15.9 years old and weighed 5.2 to 151.6 lbs. Pregnant or lactating female dogs were excluded from the study.

Experimental Design: This study was a randomized, double-masked, negative (vehicle) controlled, multi-center field effectiveness and safety study conducted in compliance with Good Clinical Practices (GCP). Dogs were randomly assigned to either receive Mometamax Single™ or the vehicle control in a 2:1 ratio.

Table II.1: Number of dogs in each treatment group.

Treatment Group	Dose	Treatment Day	Number of Dogs
Mometamax Single™	0.8 mL per affected ear	Day 0	245 (117 F, 128 M)
Vehicle Control	0.8 mL per affected ear	Day 0	127 (62 F, 65 M)

Inclusion Criteria: A dog had to be at least 12 weeks of age; have unilateral or bilateral otitis externa with a total clinical score of 6 or greater for at least one affected ear; have bacteria, yeast, or both present in the affected ear(s) as confirmed by cytology; and be physically healthy or have a stable condition not affecting its health.

Exclusion Criteria:

- Presence of an otic foreign body in affected ear(s)
- Concurrent ear mite infestation
- Evidence of a current endocrine disorder (e.g., Cushing's disease, diabetes mellitus, hypo- or hyperthyroidism)
- Known food allergy that was not well-controlled
- Systemic bacterial or fungal infection and was undergoing antimicrobial treatment
- Local infection outside of the external ear canal and pinna
- Neoplastic or non-neoplastic masses occluding the ear canal or chronic proliferative changes of the affected ear canal(s) that have occluded it (them)
- Ruptured tympanic membrane
- Known or suspected hypersensitivity to gentamicin, mometasone furoate, or posaconazole
- Ownership by clinic personnel
- Current enrollment in another clinical trial
- Pregnant or lactating
- Ear cleaning, groomer visit, swimming, or participation in other water activities in the past 7 days
- Treatment with any drugs that might have interfered with the assessment of effectiveness without an adequate washout period

Drug Administration: A 0.8-mL dose of Mometamax Single™ or vehicle control was administered once on Day 0 to the affected ear. Administration was followed by massaging the base of the ear to ensure distribution. The vehicle control had the same formulation and inactive ingredients as the test article but without the active ingredients.

Prior to treatment administration on Day 0, the entire external ear canal was cleaned with saline. Mometamax Single™ or the vehicle control was administered in the veterinary clinic by a veterinarian or veterinary technician on Day 0. Ears were not cleaned or flushed at any time during the study after the initial treatment administration on Day 0. Bilateral application was permitted at the Investigator's discretion if both ears were affected. In cases of bilateral disease, only one ear, predetermined by the protocol, was monitored as the evaluable ear.

Measurements and Observations: Dogs were evaluated over a 33-day period with clinic visits on Days 0, 7±1, 14±2, and 33±3. On evaluation days, dogs underwent physical examination, otic examination, and clinical scoring. Hearing evaluation was performed on Days 0 and 33±3 or at study withdrawal. Samples for hematology, serum chemistry, and urinalysis were collected on Days 0 and 33 (±3), and if a dog was withdrawn early from the study or if the Investigator deemed it necessary in response to an adverse event.

The primary clinical effectiveness endpoint was based on the total otitis externa score of the evaluable ear on Day 33 (actual day ranged from Day 30 to Day 36). A clinical score was calculated for each dog at each visit by totaling the scores for each of four individual clinical signs (erythema, swelling, ulceration, and exudate). The individual score for each sign was assigned based on the severity

of that sign (0=none; 1=mild; 2=moderate; 3=severe). The maximum possible total clinical score on each visit day was 12. Clinical scoring was conducted prior to the first treatment on Day 0, then on Days 7±1, 14±2, and 33±3.

Ear swabs were collected from the evaluable ears on Day 0 and cultured for the presence and quantification of *Staphylococcus pseudintermedius, Escherichia coli, Proteus mirabilis*, *Pseudomonas aeruginosa*, β-hemolytic *Streptococcus* species, *Enterococcus* species, and *Malassezia pachydermatis*. An additional ear swab was obtained at study exit from cases with clinical failure. Isolates were evaluated for their susceptibility to gentamicin and posaconazole, as appropriate.

Definition of Success/Failure: Dogs with final total clinical scores of 3 or less on Day 33, without a single individual score for one of the evaluation categories worsening as compared to Day 0, were considered treatment successes.

Statistical Methods:

The experimental unit was the designated study ear from each dog. For the analysis of effectiveness, a two-sided test was used at a significance level of 0.05. The endpoint of efficacy (treatment success) was analyzed using a generalized linear mixed model (GLMM), assuming a binomial distribution and using a logit link. The model included treatment as a fixed effect, and site and the site-by-treatment interaction as random effects. Estimated success rates, and their corresponding 95% confidence intervals (CI) were obtained by back-transforming the GLMM least squares estimates.

Descriptive analysis was conducted for total clinical scores on Day 7 by treatment group.

Results:
The effectiveness analysis included 163 dogs in the Mometamax Single™ group and 91 dogs in the vehicle control group. The success rate in Mometamax Single™ -treated dogs was 80.5%, compared to 19.6% in the vehicle control group. Table II.2 summarizes the results of the statistical analysis and shows the proportions of success in the two groups; the results are significantly different ($p<0.0001$).

Table II.2: Day 33 Effectiveness Results.

Treatment Group	Numbers of Dogs with Treatment Success	Estimated Proportion of Success*	95% Confidence Interval†
Mometamax Single™ (N=163)	123	80.5%	(68.6%, 88.6%)
Vehicle Control (N=91)	15	19.6%	(10.1%, 34.6%)

* Based on back-transformed least squares means
† Placebo vs. Mometamax Single™ $p<0.0001$
N=Number of dogs

At Visit 2 (Day 7), dogs showed a trend toward improved mean total clinical scores in the Mometamax Single™ group compared to the vehicle control group. The observed means (standard deviation) of total clinical score were 3.12 (2.02) and 5.17 (2.43) for the animals in the Mometamax Single™ group and the vehicle control group, respectively.

Microbiology:
Administration of Mometamax Single™ was shown to be effective at treating cases of otitis externa caused by *S. pseudintermedius* (84 successful cases and 25 failures), *P. aeruginosa* (15 successful cases and 11 failures), and *M. pachydermatis* (116 successful cases and 36 failures). Susceptibility data in the minimum inhibitory concentration (MIC) ranges and MIC_{50} values for *S. pseudintermedius*, *P. aeruginosa*, and *M. pachydermatis* isolates obtained on Day 0 and at withdrawal did not show any correlation between higher MICs and treatment failure. The MICs of the pathogens of interest are shown in Tables II.3 and II.4. See Table II.3 for treatment with Mometamax Single™ and Table II.4 for treatment with the vehicle control.

Table II.3: Susceptibility for gentamicin or posaconazole: MIC Range (µg/mL) [MIC_{50}[a]] of the isolates obtained at Visit 1 (Day 0) and at withdrawal (WD) from 188 evaluable canine otitis externa cases treated with Mometamax Single™.

Outcome	Study Day	*E. coli*		*Enterococcus* spp.		*P. mirabilis*		*P. aeruginosa*	
		n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]
Success	D0	7	0.25-0.50 [0.50]	*E. faecalis: 3*	4.00-8.00 [8.00]	6	0.50-8.00 [0.50]	15	2.00-8.00 [2.00]
Failure	D0	3	0.25-0.50 [0.50]	*E. avium*: 1 *E. faecalis: 4*	0.12-0.12 [0.12] 8.00-8.00 [8.00]	3	0.50-1.00 [1.00]	11	1.00-8.00 [2.00]
-	WD	1	0.50-0.50 [0.50]	*E. faecalis: 2*	4.00-8.00 [6.00]	1	0.25-0.25 [0.25]	8	1.00-32.00 [2.00]

[a] If calculable, MIC_{50} reflects the gentamicin (bacteria) or posaconazole (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described.

[b] *S. canis* was the only β-hemolytic *Streptococcus* species isolated.

D= Day, n= number, WD= withdraw

Table II.3: (Continued)

Outcome	Study Day	*S. pseudintermedius*		*S. canis* [b]		*M. pachydermatis*	
		n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]
Success	D0	84	0.06->32.0 [0.12]	8	4.00-8.00 [4.00]	116	<0.008-0.120 [<0.008]
Failure	D0	25	0.06-32.00 [0.12]	3	4.00-4.00 [4.00]	36	<0.008-0.120 [<0.008]
-	WD	16	0.06->32.0 [0.12]	2	4.00-8.00 [6.00]	21	<0.008-0.060 [<0.008]

[a] If calculable, MIC_{50} reflects the gentamicin (bacteria) or posaconazole (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described.

[b] *S. canis* was the only β-hemolytic *Streptococcus* species isolated.

D= Day, n= number, WD= withdraw

Table II.4: Susceptibility for gentamicin or posaconazole: MIC Range (µg/mL) [MIC_{50}[a]] of the isolates obtained at Visit 1 (Day 0) and at withdrawal (WD) from 99 evaluable canine otitis externa cases administered the vehicle control.

Outcome	Study Day	*E. coli*		*Enterococcus* spp.		*P. mirabilis*		*P. aeruginosa*	
		n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]
Success	D0	0	-	*E. faecalis: 1*	8.00-8.00 [8.00]	0	-	2	0.12-2.00 [1.06]
Failure	D0	7	0.25-0.50 [0.50]	*E. faecalis*: 4 *E. faecium:* 1	8.00-16.00 [8.00] 4.00-4.00 [4.00]	6	0.25-2.00 [0.50]	10	0.50-4.00 [2.00]
-	WD	4	0.25-0.25 [0.25]	*E. faecalis: 2*	4.00-8.00 [6.00]	5	0.50-2.00 [0.50]	9	0.50-4.00 [2.00]

[a] If calculable, MIC_{50} reflects the gentamicin (bacteria) or posaconazole (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described.

[b] *S. canis* was the only β-hemolytic *Streptococcus* species isolated.
D= Day, n= number, WD= withdraw

Table II.4: (Continued)

Outcome	Study Day	*S. pseudintermedius*		*S. canis* [b]		*M. pachydermatis*	
		n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]	n	MIC Range [MIC_{50}]
Success	D0	7	0.06-0.12 [0.12]	0	-	13	<0.008-0.120 [<0.008]
Failure	D0	41	0.06-32.00 [0.12]	10	4.00-8.00 [4.00]	71	<0.008-0.060 [<0.008]
-	WD	35	0.06-32.0 [0.12]	4	4.00-8.00 [6.00]	64	<0.008-0.120 [<0.008]

[a] If calculable, MIC_{50} reflects the gentamicin (bacteria) or posaconazole (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described.
[b] *S. canis* was the only β-hemolytic *Streptococcus* species isolated.
D= Day, n= number, WD= withdraw

Adverse Reactions:
The adverse reactions reported during the course of the field study are listed in Table II.5.

Table II.5: Number (%) of dogs with adverse reactions by treatment group.

Adverse Reaction	Mometamax Single™ (N=245)	Vehicle Control (N=127)
Vomiting	21 (8.6%)	4 (3.1%)
Decreased appetite	9 (3.7%)	2 (1.6%)
Pruritus	8 (3.3%)	2 (1.6%)
Ear pruritus	7 (2.9%)	1 (0.8%)
Disorientation	3 (1.2%)	0 (0.0%)

No clinically relevant treatment-related findings were noted in blood work and urinalysis.

Conclusion:
Mometamax Single™ administered once at a dose volume of 0.8 mL per affected ear is safe and effective for the treatment of otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa*) in dogs.

2. Non-Interference and Modified Checkerboard Study

Title: *In vitro* Determination of Non-Interference of Gentamicin and Posaconazole in Combination Against Canine Otitis Externa Pathogens. (Study No. S20201-00)

Study Dates: November 17, 2020 to February 18, 2021

Study Location: Fort Collins, CO

Study Design:

Objective: The objective of this *in vitro* laboratory study was to determine non-interference of combinations of gentamicin and posaconazole in the presence of mometasone furoate against bacterial and yeast isolates collected from clinical cases of canine otitis externa.

Experimental Design: Five (5) isolates each of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus pseudintermedius*, beta-hemolytic *Streptococcus* species, and *Malassezia pachydermatis* were selected from a pool of isolates from cases of canine otitis externa. Additionally, one (1) standard reference isolate per microbial species was sourced from the American Type Culture Collection (ATCC). The isolates were used to determine minimal inhibitory concentrations (MIC) for gentamicin, posaconazole, and mometasone furoate. Fractional inhibitory concentration index (FICI) determinations were calculated from MICs obtained from a modified checkerboard evaluation of a combination of active ingredients representative of the final product formulation.

Results: There was little to no activity of gentamicin (MICs≥16 µg/mL) and mometasone furoate (MICs≥8 µg/mL) against any *M. pachydermatis* isolates. Posaconazole MICs against *M. pachydermatis* ranged from 0.004-0.008 µg/mL with an MIC_{50} of 0.004 µg/mL and an MIC_{90} of 0.008 µg/mL. There was no activity of posaconazole (MICs>1 µg/mL) or mometasone furoate (MICs>16 µg/mL) against any *E. coli* isolate. Gentamicin MICs against *E. coli* ranged from 0.25-1 µg/mL with an MIC_{50} of 0.5 µg/mL and an MIC_{90} of 1 µg/mL. There was no activity of posaconazole (MICs>1 µg/mL) or mometasone furoate (MICs>16 µg/mL) against any *P. aeruginosa* isolate. Gentamicin MICs against *P. aeruginosa* ranged from 2-4 µg/mL with an MIC_{50} of 2 µg/mL and an MIC_{90} of 4 µg/mL. There was no activity of posaconazole (MICs>1 µg/mL) or mometasone furoate (MICs>16 µg/mL) against any *S. pseudintermedius* isolate. Gentamicin MICs against *S. pseudintermedius* ranged from 0.12-0.25 µg/mL with an MIC_{50} of 0.12 µg/mL and an MIC_{90} of 0.25 µg/mL. There was no activity of posaconazole (MICs>1 µg/mL) or mometasone furoate (MICs>16 µg/mL) against any beta-hemolytic *Streptococcus* spp. Gentamicin MICs against beta-hemolytic *Streptococcus* spp. ranged from 4-8 µg/mL with an MIC_{50} of 4 µg/mL and an MIC_{90} of 8 µg/mL.

When testing the combination of active ingredients in a ratio representative of the final product formulation, the MIC_{50} of the individual active compounds remained the same for each organism and each individual MIC was within one

doubling dilution of the initial MIC value. Results for the combination of active ingredients were as follows:

- Gentamicin/posaconazole: All six isolates of each microbial species (*M. pachydermatis*, *E. coli*, *P. aeruginosa*, *S. pseudintermedius*, and beta-hemolytic *Streptococcus* spp.) showed an indifferent/autonomous FICI.
- Gentamicin/mometasone furoate: All six isolates of each microbial species (*M. pachydermatis*, *E. coli*, *P. aeruginosa*, *S. pseudintermedius*, and beta-hemolytic *Streptococcus* spp.) showed an indifferent/autonomous FICI.
- Posaconazole/mometasone furoate: All six isolates of each microbial species (*M. pachydermatis*, *E. coli*, *P. aeruginosa*, *S. pseudintermedius*, and beta-hemolytic *Streptococcus* spp.) showed an indifferent/autonomous FICI.

Conclusions: Results of *in vitro* tests to determine FICIs demonstrated a lack of interference between the three active ingredients. MICs indicated that gentamicin is active against *E. coli*, *P. aeruginosa*, *S. pseudintermedius*, and beta-hemolytic *Streptococcus* spp. and posaconazole is active against *M. pachydermatis*.

III. TARGET ANIMAL SAFETY

The safety of Mometamax Single™ was demonstrated in a well-controlled laboratory margin of safety study in puppies that included elevated doses and an exaggerated dosing regimen.

A. Margin of Safety Study

Title: Gentamicin – Mometasone Furoate – Posaconazole Otic Suspension: A 1-Month Target Animal Safety Study in Young Puppies Dosed Once Every Two Weeks by the Intra-aural Route. (Study No. 20102923)

Study Dates: November 15, 2017 to May 20, 2020

Study Location: Spencerville, OH

Study Design:

Objective: To assess the safety of Mometamax Single™ administered to puppies at 1X, 3X, and 5X the maximum labeled dose of 0.8 mL/ear three times at two-week intervals.

Study Animals: Thirty-two (32) healthy Beagle puppies (16 males and 16 females), 11- to 12- weeks of age and 2.8 to 5.0 kg body weight at first treatment.

Experimental Design: Puppies were randomized to one of four treatment groups of eight dogs per group (four per sex). Puppies were administered Mometamax Single™ in both ears at 1X, 3X, or 5X the maximum labeled dose, or mineral oil (control group, or 0X) at the same dose volume as the 5X group, three times at two-week intervals (Days 1, 15, and 29). Puppies were randomly assigned to two cohorts

to permit staggering of the study start and necropsy by one day. The study was conducted in accordance with the FDA Good Laboratory Practice Regulations.

Table III.1: Treatment Groups.

Group	Dose per ear (mL)	Total dose volume (mL)	Number and sex of animals
Control (0X)*	4.0	8.0	4 males, 4 females
1X	0.8	1.6	4 males, 4 females
3X	2.4	4.8	4 males, 4 females
5X	4.0	8.0	4 males, 4 females

*Control article was mineral oil

Drug Administration: Mometamax Single™ or mineral oil (control article) was administered to both ears of each animal by instillation into the ear canal. Due to the volume limitation of the ear canal, dose volumes for the 0X, 3X, and 5X groups were administered in separate 0.8 mL/ear applications staggered by a minimum interval of two hours between each application. Following dosing, the head of the dog was restrained for approximately two minutes to prevent the dog from shaking its head.

Measurements and Observations: Clinical observations were conducted daily throughout the study and at least three times through 5-6 hours post-dose on dosing days. Veterinary physical examinations were conducted on Days -7/-8, -1, 2, 16, and 30 (approximately 24 hours after the first instillation on Days 1, 15, and 29). Body weights were recorded on Days -12/-13, -7/-8, -5/-6, -1, 1, 8, 15, 22, 29, and 31 (day of necropsy). Individual food consumption was measured daily starting on Day -7/-8. Otoscopic examinations and hearing assessments were performed pre-treatment and on Days 2, 16, and 30. Ophthalmic and electrocardiography examinations were performed pre-treatment and on Day 30. Clinical pathology parameters (hematology, coagulation profile, clinical chemistry, urinalysis, fecal evaluation) were evaluated pre-treatment and on Days 2 and 31/30. Response to Adrenocorticotropic Hormone (ACTH) stimulation was evaluated pre-treatment and on Day 30. All dogs were euthanized on Day 31 and underwent full necropsy, organ weight determination, and histopathological evaluation.

Statistical Methods:

The individual dog was the experimental unit.

Absolute and calculated (ratios) organ weights were analyzed using analysis of variance (ANOVA) with dose, sex, and the sex-by-dose interaction as fixed effects, and block as a random effect.

Body weight, heart rate, respiratory rate, rectal temperature, food consumption (weekly average), serum chemistry, coagulation, hematology, and urinalysis were analyzed using repeated measures analysis of covariance (RMANCOVA) with dose, sex, time, as well as the two-way and three-way interactions as fixed effects, and cohort as a random effect. The pre-dose (or nearest to Day 1 if there are multiple values) values were used as a covariate in the model.

All fixed model effects were tested at a two-sided significance level α = 0.10 except for the three-way treatment-by-sex-by-treatment day interaction, which was tested at α =0.05. Pairwise mean comparisons between each treatment against the control group are also performed using an unadjusted α = 0.10.

Results: No test article-related effects were observed on survival, clinical observations, veterinary physical examinations, body weights, food consumption, otoscopic examinations, hearing assessments, ophthalmic examinations, coagulation, clinical chemistry, urinalysis, fecal evaluations, electrocardiography parameters, or gross pathology.

Mometamax Single™ administration was associated with mild eosinopenia in the 3X and 5X groups and suppression of serum cortisol levels. On Day 30 prior to ACTH administration, two of eight dogs in the 1X group had below normal cortisol levels, all dogs in the 3X group had cortisol levels of <0.2 µg/dL, and all dogs in the 5X group had below normal cortisol levels (seven having a cortisol level of <0.2 µg/dL). All dogs in the 1X group had normal post-ACTH stimulation cortisol response levels. Seven of eight dogs in each of the 3X and 5X groups had suppressed ACTH stimulation responses but remained in normal reference range. The low baseline and post-ACTH stimulation test cortisol levels correlated with the pathology results of lower mean adrenal weights and mild atrophy of the adrenal cortex in the 3X and 5X groups. The mean adrenal weights in 3X and 5X group females and the 5X group males were statistically lower than control values. Mild adrenal atrophy in the zona fasciculata was dose-dependent in incidence and magnitude in 3X and 5X group females. Histopathology demonstrated mild atrophy of the external auditory canal epidermis and mild atrophy of the external surface of the tympanic membrane in the 1X, 3X, and 5X groups. One male in the 3X group and one male in the 5X group had a minimal epidermal erosion/ulcer in the external auditory canal of one ear, whereas this finding was not noted in the control or 1X treatment groups.

Conclusion: This study supports the safe use of Mometamax Single™ at the recommended clinical dose of 0.8 mL per affected ear(s) in dogs. Mometamax Single™ administration at the recommended clinical dose was associated with lower baseline cortisol in two of eight dogs but normal ACTH response in all dogs. Doses of 3X and 5X the recommended clinical dose were associated with eosinopenia, and alterations in the hypothalamic-pituitary-adrenal axis as evidenced by the ACTH stimulation test and adrenal cortex pathology results. Mometamax Single™ administration was also associated with minimal to mild atrophy of the external auditory canal epidermis and of the external surface of the tympanic membrane. The results of this study are consistent with systemic absorption of mometasone furoate resulting in suppression of the hypothalamic-pituitary-adrenal axis as seen with administration of exogenous corticosteroids.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Mometamax Single™:

USER SAFETY WARNINGS:

Not for human use. Keep this and all drugs out of the reach of children. In case of accidental ingestion by humans, contact a physician immediately. In case of accidental skin contact, wash area thoroughly with water. Avoid contact with eyes. If contact with the eyes occurs, flush thoroughly with water for at least 15 minutes. If wearing contact lenses, rinse eyes first then remove the contact lenses and continue to rinse. If symptoms develop, seek medical advice. Humans with known hypersensitivity to gentamicin, posaconazole, and/or mometasone furoate should avoid handling this product.

VI. 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. The data demonstrate that Mometamax Single™, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose otitis externa and prescribe appropriate treatment.

B. Exclusivity

Mometamax Single™, as approved in our approval letter qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Mometamax Single™.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.