Date of Approval: April 10, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-598

Otiserene®

(marbofloxacin, terbinafine, and dexamethasone otic suspension)

Dogs

Otiserene® is indicated for the treatment of otitis externa associated with susceptible strains of yeast *(Malassezia pachydermatis)* and bacteria *(Staphylococcus pseudintermedius)* in dogs.

Sponsored by:

Dechra, Ltd.

Executive Summary

Otiserene® (marbofloxacin, terbinafine, dexamethasone otic suspension) is approved for the treatment of otitis externa associated with susceptible strains of yeast *(Malassezia pachydermatis)* and bacteria *(Staphylococcus pseudintermedius)* in dogs.

Otiserene® is an otic suspension with three active ingredients: an antibacterial (marbofloxacin), antifungal (terbinafine), and anti-inflammatory (dexamethasone). One dose (1 tube) 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 be cleaned for 30 days afterwards.

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 clinical signs: erythema, exudate, swelling, and ulceration. 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, culture samples 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 Otiserene® or vehicle control to the dogs' affected ear or ears on Day 0. (The vehicle control had the same formulation and inactive ingredients as Otiserene® but without the active ingredients.)

A dog was considered a treatment success if the overall clinical otitis score was ≤3 on Day 30 (+2) 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 (71.3% versus 26.3%). The culture results showed that Otiserene® was successful at treating cases of otitis externa caused by *M. pachydermatis* and/or *S. pseudintermedius*. Adverse reactions seen in dogs in the study included anorexia or decreased appetite, pruritus, vomiting, and conjunctivitis or eye inflammation.

The sponsor conducted an *in vitro* laboratory study that demonstrated that the presence of dexamethasone does not interfere with the activity of the two microbiologically active ingredients, marbofloxacin and terbinafine, 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 of all bacterial and yeast quality control organisms were within the Clinical and Laboratory Standards Institute's acceptable ranges for marbofloxacin and terbinafine, as appropriate for the particular organism.

The sponsor also conducted a margin of safety laboratory study in young, healthy, intact male and female beagles. The dogs were administered Otiserene® in both ears on 3 dosing days, 14 days apart, at 0X, 1X, 3X, and 5X the label dose. All dogs remained healthy with normal hearing throughout the study. Adverse reactions in the treatment groups included decreased leukocytes, lymphocytes, monocytes, and globulins;

decreased fibrinogen and activated partial thromboplastin time; bilateral adrenal gland atrophy; decreased bone marrow cellularity; increased glycogen vacuolation; epidermal atrophy in external ear canals; and thymic atrophy. The observations were attributed to the systemic effects of the dexamethasone in Otiserene®.

User Safety
The labeling for Otiserene® 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 Otiserene®, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-598

B. Sponsor

Dechra, Ltd.
Snaygill Industrial Estate
Keighley Rd.
Skipton, North Yorkshire
BD23 2RW, United Kingdom

Drug Labeler Code: 043264

U.S. Agent Name and Address:

Dr. Samantha O'Brien
Dechra Ltd
7015 College Blvd, Suite 510
Overland Park, KS 66211

C. Proprietary Name

Otiserene®

D. Drug Product Established Name

marbofloxacin, terbinafine, dexamethasone otic suspension

E. Pharmacological Category

Antibacterial, antifungal, anti-inflammatory

F. Dosage Form

Otic suspension

G. Amount of Active Ingredient

15.1 mg marbofloxacin, 22.7 mg terbinafine, 2.01 mg dexamethasone per tube

H. How Supplied

A 10 count carton containing 10 pouches with 1 single use tube and applicator tip.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Otiserene® should be administered by veterinary personnel. Verify the tympanic membrane is intact prior to administration. Clean and dry the external ear canal before administering the product. Administer one dose (1 tube) per affected ear once. Do not clean the ear canal for 30 days after administration.

K. Route of Administration

Otic

L. Species/Class

Dog

M. Indication

Otiserene® is indicated for the treatment of otitis externa associated with susceptible strains of yeast *(Malassezia pachydermatis)* and bacteria *(Staphylococcus pseudintermedius)* in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

The dose of one tube administered to the external ear canal once was selected for the treatment of otitis externa in dogs based upon the ear wash depletion study (PAH-004), the Minimum Inhibitory Concentration (MIC) data of marbofloxacin, and existing MIC data of terbinafine. The ear wash depletion study was conducted in 12 dogs with normal ears to estimate the duration of activity of the three active ingredients in Otiserene®. On Day 0, dogs were administered 1.1 mL of Otiserene® in both ears. On Days 10, 15, and 21, four dogs were selected, and both ears were flushed with 15 mL of the prepared ear wash solution. Each ear was analyzed as a separate sample for concentrations of marbofloxacin, terbinafine, and dexamethasone using a validated high performance liquid chromatography with tandem mass spectroscopy detection (HPLC-MS/MS) method. Linear regression was used to estimate the number of days needed to reach the lower limit of quantification for each of the three analytes. In order to maximize the inferential value associated with the small sample size, prediction intervals (95% confidence intervals) were generated. The upper bound of the 95% prediction interval for marbofloxacin to fall below 0.5 µg/mL (500 ng/mL) was extrapolated at approximately 39 days. The median log of the marbofloxacin to fall below 0.5 µg/mL (500 ng/mL) was extrapolated at 27 days. It is presumed that the depletion of the drug is faster in ears affected with otitis externa due to increased absorption through the disrupted skin barrier and drug degradation secondary to inflammation. Therefore, a final day of evaluation of Day 30 (+2) included in the study to support substance evidence of effectiveness was chosen between the median log and upper 95% confidence interval.

B. Substantial Evidence

1. Field Study

Title: Clinical Evaluation of the Safety and Efficacy of a Marbofloxacin, Terbinafine Hydrochloride, and Dexamethasone Combination Otic Suspension for the Treatment of Otitis Externa in Dogs. (Study No. PAH21-006)

Study Dates: September 20, 2021 to April 17, 2024

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

Concord, NC	Springfield, MO
Newton, NC	Franklin, IN
Arcanum, OH	Oxford, OH
Mount Vernon, WA	Houston, TX
Dallas, TX	Smithfield, NC
Ocala, FL	Greenwich, NY
Columbia, SC	Zachary, LA
Virginia Beach, VA	Lawrence, KS
Aumsville, OR	Port Orchard, MI
Battle Creek, MI	

Study Design:

Objective: The objective of the study was to evaluate the field safety and effectiveness of a single administration of Otiserene® for the treatment of otitis externa in dogs. The safety analysis was based on the evaluation of clinical pathology parameters and occurrence of adverse events during the study.

Study Animals: Two hundred and thirty-two client-owned dogs diagnosed with otitis externa were enrolled in the study (155 treated with Otiserene®, 77 control) and were included in the safety analysis. Of the 232 enrolled dogs, 172 dogs were considered suitable for inclusion in the effectiveness population (115 treated with Otiserene®, 57 control). The dogs enrolled were 3.6 months to 14.5 years old and weighed 5.8 to 170 pounds. Pregnant or lactating female dogs were excluded from the study.

Experimental Design: This study was a multicentered, vehicle controlled, randomized, masked field effectiveness and safety study conducted in compliance with Good Clinical Practice. The dogs in the study were randomized in a 2:1 ratio to the Otiserene® or the vehicle control groups.

Table II.1: Treatment Groups.

Treatment Group	Dose	Treatment Day	Number of Dogs
Otiserene®	1 mL per affected ear	Day 0	155
Control (vehicle)	1 mL per affected ear	Day 0	77

Inclusion Criteria: To enroll in the study, a dog had to be at least 12 weeks of age or older, have intact tympanic membranes, and have a minimum total clinical otitis score of 6 out of possible 12, in at least one ear, based on the following signs of otitis externa: erythema, exudate, swelling, and ulceration. Each clinical sign of otitis externa was scored as: none (0), mild (1), moderate (2), or severe (3). If the otitis externa infection was bilateral with both ears having a minimum score of 6, the right ear became the designated ear for evaluation regardless of the score of the left ear.

Exclusion Criteria:

- Total clinical otitis score less than 6 in both ears
- Concurrent *Otodectes cynotis* infection
- Presence of otic foreign body
- Ruptured tympanic membrane
- Stenotic or calcified ear canals
- Evidence of head tilt
- Cranial neurologic disease or signs of poor general health
- Cutaneous manifestations of cancer or auto-immune disease
- Received topical or oral antifungals (including ear washes) within the previous 30 days
- Treated with systemic or topical antimicrobials within the previous 17 days
- Treated with long-acting antimicrobials within the previous 30 days
- Treated with antihistamines or anti-inflammatories within the previous 17 days
- Treated with long-acting corticosteroids within the previous 28 days
- Treated with a depot form of corticosteroids within the previous 4 months
- Pregnant or lactating
- Dogs owned by the sponsor or site employee

Drug Administration: A 1 mL dose of Otiserene® or vehicle control was administered once on Day 0 to the infected ear. 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 affected ear canal(s) were cleaned with saline. Ears were not cleaned or flushed at any other time during the study or after the initial administration of treatment on Day 0. Otiserene® or vehicle control was administered in the veterinary hospital on Day 0. Treatment

was applied topically to the ear canal(s), followed by massaging the base of the ear. Bilateral application was allowed if both ears were affected but effectiveness was based on the evaluation of only one ear.

Measurements and Observations: Dogs were evaluated over a 30-day period with clinic visits on Days 0, 10 (+2), 20 (+2), and 30 (+2). On evaluation days, dogs underwent a physical examination, otic examination, clinical scoring, and hearing evaluation. Samples for hematology, serum chemistry, and urinalysis were collected on Days 0 and 30 (+2), and if the dog was withdrawn from the study early or when the Investigator deemed necessary in response to an adverse event.

On Day 0, samples were collected from the external ear canal of the affected ear(s) and cultured for the presence and semi-quantification of the targeted pathogens: *Malassezia pachydermatous* (yeast)*, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus pseudintermedius,* and β-hemolytic *Streptococcus* (bacteria). Susceptibility testing was conducted on Day 0 isolates, on Day 30 (+2) isolates if a clinical cure was not achieved at the final visit (clinical otitis score ≥4), and from isolates collected from dogs withdrawn due to perceived lack of effectiveness (improvement ≤2 compared to baseline).

Definition of Success/Failure: The endpoint for effectiveness was improvement in the clinical otitis score of the designated study ear at the Day 30 (+2) visit compared to the baseline clinical otitis score on Day 0. A Day 30 (+2) clinical otitis score of ≤3, along with no clinical score getting worse was considered a treatment success.

Statistical Methods:
The experimental unit was the designated study ear from each dog.
Efficacy Analysis: 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-transformation from the GLMM least squares estimates.

Safety Analysis: Treatment effects on the safety parameters were evaluated at alpha = 0.10. Urinalysis outcomes were summarized as appropriate, but no hypothesis testing was conducted. Physical examination variables were analyzed using repeated measures analysis of covariance (RMANCOVA) with treatment, day, and the day-by-treatment interactions as fixed effects, and site and the site-by-treatment interaction as random effects. Pre-treatment values were used as a covariate. Hematology and serum chemistry variables were analyzed using analysis of covariance (ANCOVA) with treatment, day, and the day-by-treatment interactions as fixed effects, and site and the site-by-treatment interaction as random effects. Pre-treatment values were used as a covariate.

Results:
There were 115 Otiserene®-treated, and 57 control dogs included in the assessment of effectiveness. The proportion of dogs that were treatment successes in the Otiserene® treated group was significantly different from (p=0.0001) and greater than the control group. See Table II.2 below.

Table II.2. Estimated Proportion of Dogs Achieving Treatment Success on Day 30.

Treatment	Number of Dogs with Treatment Success	Estimated Proportion of Success*	95% Confidence Interval
Otiserene® (N=115)	82	74.9	(61.3, 84.9)
Control (N=57)	15	27.7†	(14.9, 45.5)

* Based on back-transformed least squares means
† Control vs Otiserene® p=0.0001
N=Number of dogs

Microbiology:
A total of 228 samples were collected and submitted from dogs which met the inclusion criteria for the effectiveness evaluation. One hundred and seventy-two (172) samples were collected on Day 0, and 71 samples were collected at Study Exit (SE) which included samples taken from Day 30 and unscheduled visits (Tables 1a and 1b). Cultures from the 172 Day 0 swab samples resulted in the isolation of *M. pachydermatis* (n=141, 82.0%), *S. pseudintermedius* (n=88, 51.2%), *P. mirabilis* (n=13, 7.6%), *P. aeruginosa* (n=13, 7.6%), and *S. canis* (n=20, 11.6%). Only dogs with *S. pseudintermedius* and/or *M. pachydermatis* present upon culture had 10 or more cases successfully treated with Otiserene®.

Otiserene® was successful at treating cases caused by the targeted pathogens with a range of marbofloxacin and terbinafine susceptibilities including those with decreased susceptibility. An evaluation of the susceptibility profiles of isolates taken on Day 0 and at SE is provided in Tables II.2 and II.3. Notable findings include four different cases that were successfully treated with Otiserene® that had marbofloxacin-resistant *P. mirabilis, P. aeruginosa*, or *S. pseudintermedius* present on Day 0. There were also three Otiserene®-treated cases with low marbofloxacin MICs of *S. pseudintermedius* (0.25 µg/mL) on Day 0, and increased MICs of recovered *S. pseudintermedius* isolates at SE (16, 16, and 32 µg/mL). Whether selection of antimicrobial resistance occurred in these cases was not verified; this was not observed in the control group.

Table II.3. Frequency of isolates obtained from 172 evaluable canine otitis externa cases included in the effectiveness evaluation upon entry at Visit 1 (D0) and at Study Exit (SE). Pathogens with 10 or more cases successfully treated.

Treatment	Effectiveness Outcome	Sample	*S. pseudintermedius* (%)	*M. pachydermatis* (%)
Otiserene®	Success (82 total)	D0	48.8	86.6
	Failure (33 total)	D0	53.1	81.3
		SE	50.0	62.5
Control	Success (15 total)	D0	40.0	93.3
	Failure (42 total)	D0	59.5	71.4
		SE	47.6	59.5

Table II.4. Frequency of isolates obtained from 172 evaluable canine otitis externa cases included in the effectiveness evaluation upon entry at Visit 1 (D0) and at SE. Pathogens with less than 10 cases successfully treated.

Treatment	Effectiveness Outcome	Sample	*S. canis* (%)	*P. mirabilis* (%)	*P. aeruginosa* (%)
Otiserene®	Success (82 total)	D0	6.1	3.7	4.9
	Failure (33 total)	D0	21.9	15.6	12.5
		SE	18.8	3.1	6.3
Control	Success (15 total)	D0	6.7	6.7	0.0
	Failure (42 total)	D0	16.7	9.5	11.9
		SE	11.9	7.1	14.3

Table II.5. Marbofloxacin and terbinafine (*M. pachydermatis*) MICs (µg/mL) from isolates obtained from 115 evaluable Otiserene®-treated cases included in the effectiveness evaluation upon entry at Visit 1 (D0) and at SE.

Effectiveness Outcome	**Sample**	***SP****	***SC****	***PM****	***PA****	***MP****
Success (82 total)	D0	0.12-32 (n=40)	1-4 (n=5)	0.06-4 (n=3)	0.25-4 (n=4)	0.03-1 (n=71)
Failure (33 total)	D0	0.12-32 (n=18)	1-4 (n=7)	0.06-8 (n=5)	0.5-32 (n=4)	0.008-0.5 (n=25)
	SE	0.12-32 (n=16)	1-4 (n=6)	0.06 (n=1)	0.5-32 (n=2)	0.008-0.5 (n=20)

* SP = *S. pseudintermedius,* SC = *S. canis*, PM = *P. mirabilis*, PA = *P. aeruginosa*, MP = *M. pachydermatis*.

Table II.6. Marbofloxacin and terbinafine (*M. pachydermatis*) MICs (µg/mL) from isolates obtained from 57 Control-treated cases included in the effectiveness evaluation upon entry at Visit 1 (D0) and at SE.

Effectiveness Outcome	**Sample**	***SP****	***SC****	***PM****	***PA****	***MP****
Success (15 total)	D0	0.25 (n=6)	1 (n=1)	0.06 (n=1)	ND**	0.06-0.25 (n=10)
Failure (42 total)	D0	0.12-0.5 (n=25)	1 (n=8)	0.06-0.12 (n=2)	0.5-1 (n=5)	0.03-0.5 (n=29)
	SE	0.25-0.5 (n=20)	1-2 (n=5)	0.06-0.12 (n=3)	0.5-4 (n=6)	0.03-2 (n=24)

*SP = *S. pseudintermedius,* SC = *S. canis*, PM = *P. mirabilis*, PA = *P. aeruginosa*, MP = *M. pachydermatis; **ND= no data*

Adverse Reactions:
The adverse reactions reported during the course of the field study are listed in Table II.7.

Table II.7. Number (%) of dogs with adverse reactions by treatment group.

Adverse Reaction	Otiserene® (n=155)	Control (n=77)
Anorexia/decreased appetite	6 (3.8%)	2 (2.5%)
Pruritus	4 (2.6%)	1 (1.3%)
Vomiting	3 (1.9%)	0 (0.0%)
Conjunctivitis/eye inflammation	2 (1.2%)	0 (0.0%)

Conclusion: Otiserene® administered as a single intra-auricular dose 1 mL per affected ear in dogs with otitis externa was safe and effective for the treatment of otitis externa with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*) in dogs.

2. Non-Interference and Susceptibility Studies

Title: *In vitro* Determination of Non-interference of Terbinafine, Marbofloxacin, and Dexamethasone in Combination Against Canine Otitis Externa Pathogens. (Study No. MR2408)

Study Dates: April 1, 2024 to April 5, 2024

Study Location: Fort Collins, CO

Purpose and Procedures:
The objective of this laboratory study was to determine *in vitro* non-interference of combinations of terbinafine and marbofloxacin in the presence of dexamethasone against bacterial and yeast isolates collected from clinical cases of canine otitis externa.

Isolates:
Bacterial and yeast isolates were selected from clinical cases of otitis externa in dogs. Ten isolates each of *Malassezia pachydermatis, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus pseudintermedius*, and β-hemolytic *Streptococcus* species were included in this study. Additionally, one American Type Culture Collection (ATCC) strain of each organism type was tested. Each clinical isolate was identified to the species level. The bacterial and yeast isolates were selected based on their previously determined individual MICs.

Preparation of Fractional Inhibitory Concentration Index (FICI) Susceptibility Panels:
Non-interference determination was calculated from MICs obtained from a modified standard checkerboard evaluation of the combination of terbinafine and marbofloxacin in the presence of dexamethasone. The susceptibility testing included 11 isolates of each species or group as previously mentioned (10 field strains and one ATCC strain).

Broth microdilution, 96-well microtiter plates were prepared with cation-adjusted Mueller Hinton Broth (CAMHB) as recommended by the Clinical and Laboratory Standards Institute (CLSI) VET01 standard for all bacteria with the exception of the *Streptococcus* spp. which were tested using CAMHB with 3% lysed horse blood (LHB). Each well of the MIC plate contained 100 µL of prepared dilutions. Roswell Park Memorial Institute-1640 medium buffered with 0.165 mol/L MOPS, 20 g/L glucose, 4 g/L bile salts, 1 mL/L glycerol, and 0.4 mL/L Tween 20 (RPMIMZ) was used for MIC plate preparation for yeast testing. Each well of the MIC plates contained 100 µL of the prepared dilutions. The RPMIMZ dilutions were initially prepared at 2X the final concentration to account for the 1:2 dilution during the inoculation process.

Antimicrobial concentrations tested were prepared based upon the active ingredient (i.e., marbofloxacin MIC for bacteria or the terbinafine MIC for yeast). Susceptibility plates were prepared including all three compounds individually, as well as in combination. The intended ratio of the active ingredients of 1.5:1.0:0.14 (terbinafine: marbofloxacin: dexamethasone, respectively) was tested. The following combinations were tested: terbinafine/marbofloxacin, marbofloxacin/dexamethasone, terbinafine/dexamethasone, and terbinafine/marbofloxacin/dexamethasone.

Concentrations of active ingredients in the combination plates encompassed at least three two-fold dilutions above and below the modal MIC determined for the test isolates using the most active antimicrobial.

Results:
For the combination of terbinafine and marbofloxacin, no antagonism was seen for any isolate. All isolates showed indifference.

No antagonism was measured for the combination of marbofloxacin and dexamethasone. All bacterial isolates showed indifference with this combination. A Fractional Inhibitory Concentration Index (FICI) was not calculated for yeast as both compounds were inactive.

For the combination of terbinafine and dexamethasone, all yeast isolates showed indifference. The bacterial FICI calculations were not performed as both compounds were inactive.

No antagonism was measured for the combination of terbinafine and marbofloxacin in the presence of dexamethasone. All bacterial and yeast isolates showed indifference with this combination.

Quality Control:
The MICs of all bacterial and yeast quality control organisms were within the CLSI's acceptable ranges for marbofloxacin and terbinafine, as appropriate for the organism.

All inoculum levels were within the acceptable range.

Conclusion: All results of *in vitro* tests to determine FICIs demonstrated a lack of interference between and indifference with the two microbiologically-active ingredients. Tests including dexamethasone in combination showed indifference and a lack of interference with two microbiologically-active ingredients.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: Target Animal Safety Study of MTD Otic Suspension in Dogs. (Study No. PAH21-005)

Study Dates: October 10, 2021 to October 20, 2022

Study Location: Stouffville, ON, Canada

Study Design:

Objective: This laboratory study evaluated the safety of the test article (MTD Otic Suspension) when administered aurally to dogs on three separate dosing days, 14 days apart, at 0X, 1X, 3X, and 5X the maximum proposed label dose.

Study Animals: Thirty-six (18 male, 18 female) Beagle dogs, four-months of age and weighing 3.8-6.3 kg at enrollment, were used for the study.

Experimental Design: This study was a placebo-controlled, randomized, masked laboratory study conducted in accordance with Good Laboratory Practice (GLP) regulations. Thirty-two dogs were randomized to four study groups stratified by sex.

Table III.1. Treatment Groups

Group	Number of Dogs	Article	Total Volume per Dog (mL)	Dosing Sessions per Dog[1]	Route	Administration Days
T0	4M,4F	Vehicle Otic Suspension	10	5	Aural	0, 14, 28
T1 (1X)	4M,4F	Otiserene®	2	1	Aural	0, 14, 28
T3 (3X)	4M,4F	Otiserene®	6	3	Aural	0, 14, 28
T5 (5X)	4M,4F	Otiserene®	10	5	Aural	0, 14, 28

M = male, F = female
[1]In each dosing session, a maximum of 1 mL per ear was administered. For dogs requiring multiple dosing sessions to provide full intended volumes (groups T0, T3, and T5), sessions were separated by a period of 2 hrs±15 min.

Drug Administration: Dosing via aural administration with equal dose in both ears was performed on three separate dosing days 14 days apart. For dogs requiring multiple dosing sessions to provide full intended volumes (groups T0, T3, and T5), sessions were separated by a period of 2 hrs±15 min.

Measurements and Observations: Safety variables assessed in this study included: clinical observations, physical examinations, otic evaluations, behavior evaluations, body weight measurements, food consumption, clinical pathology and urinalysis evaluations, ACTH stimulation test, gross necropsy, and histopathology evaluations.

Study procedures and measurements occurred as follows:

- Clinical observations were conducted twice daily throughout the study, with the exception of observations on dosing days, and once on euthanasia days. Observations were conducted five times daily on dosing days.
- Physical examinations, including ocular examinations, otic evaluations, and hearing tests, were performed twice during acclimation, four times during the testing phase, and once prior to euthanasia.
- Body weights were measured eight times during acclimation, twelve times during the testing phase, and once prior to euthanasia.
- Food consumption was measured once daily throughout the study.
- Blood was collected for hematology, clinical chemistry, and coagulation once during acclimation, once during the testing phase, and once prior to euthanasia.
- Urine was collected for urinalysis once during acclimation, once during the testing phase, and once prior to euthanasia.
- ACTH stimulation testing was performed once during acclimation (Day -5), once during the testing phase (Day 1), and once prior to euthanasia (Day 28).
- Behavioral assessments were performed once daily throughout the study, starting on Day-7, with the exception on dosing days. Behavioral assessments were performed five times daily on dosing days.

Statistical Methods:

The individual dog was the experimental unit.

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

The data from ACTH stimulation test was analyzed using ANCOVA with dose, sex, and the sex-by-dose interaction as fixed effects, and the pre-treatment value as the covariate.

Body weight, clinical chemistry, coagulation, food consumption (weekly average), hematology, heart rate, respiratory rate, rectal temperature, and urinalysis were

analyzed using RMANCOVA with dose, sex, time, and the two-way and three-way interactions as fixed effects, and pre-dose (or nearest to first dose if there are multiple values) values were used as a covariate.

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

Results:
All dogs were in good health with normal hearing throughout the study and survived to study conclusion.

Clinical Observations: Epiphora, unilateral or bilateral, was observed in a large number of dogs across all dose groups (4 of 8 control dogs in 1X, 5 of 8 dogs in 3X, and 3 of 8 dogs in 5X), including the 4 of 8 control dogs, during both acclimation (13 dogs prior to dosing) and the testing phase of the study. Vomiting was observed in all treatment groups infrequently during the testing phase of the study and episodes were isolated and sporadic in occurrence.

Food consumption: Transient increases in food consumption were observed in the 1X, 3X, and 5X treatment groups compared to the control group. Food consumption values between control and treated groups during Week 1 were significantly higher in the 1X, 3X, and 5X groups. During Weeks 2 and 4 a reduction in food consumption values was noted in the 1X, 3X, and 5X groups compared to the controls. Food consumption values in Week 3 were significantly higher in the1X, 3X, and 5X groups as compared to values in the control group. There was a dose proportional effect associated with increased food consumption.

Body Weight: On the final day, in general, a reduction in body weight was observed at the end of the study in a number of dogs, across all dose groups (4 of 8 control dogs, 5 of 8 1X dogs, 5 of 8 3X dogs, and 5 of 8 5X dogs) and was slightly more prominent in female dogs. The largest reductions in body weight were seen in one 1X dog, one 3X dog, and two 5X dogs at 12%, 13%, and 10% body weight loss, respectively.

Hematology: White blood cell (WBC) values on Day 27 were significantly lower in the 3X and 5X groups as compared to the control group. Lymphocyte and monocyte counts on Day 27 were significantly lower in the 3X and 5X groups as compared to the control group.

Serum Chemistry: Globulin values on Day 27 were significantly lower in the 1X, 3X, and 5X groups as compared to the control group but remained within normal limits.

Clotting times: Fibrinogen values in males were significantly lower in the 1X and 3X groups as compared to the control group but remained within normal limits. In females, no differences were identified between groups. Activated Partial Thromboplastin Time (APTT) values were significantly lower in the 3X and 5X groups as compared to the control group but also remained within normal limits.

Necropsy and Histopathology: Bilateral adrenal gland atrophy (i.e., narrowing) of the cortical zona fasciculata layer was observed in males in the 3X and 5X groups and females in 5X group. In females, adrenal gland weights were significantly lower in the 1X, 3X, and 5X groups as compared to weights in the control group.

A microscopic decrease in bone marrow cellularity (minimal to mild), characterized by reduction in the proportion of hematopoietic tissue in relation to the amount of adipose tissue, occurred in males in the 3X and 5X groups, and in females in the 1X, 3X, and 5X groups.

Increased glycogen vacuolation of the liver (minimal to marked) relative to controls was observed in males and females in the 1X, 3X, and 5X groups. Liver weights in the 1X, 3X, and 5X groups were significantly higher than weights in the control group.

Epidermal atrophy of the left and right external (auricular) ear canals (minimal to mild) was identified microscopically exclusively in males and females in the 1X, 3X, and 5X groups.

Thymic atrophy (minimal to mild), characterized microscopically by decreased lymphocytes and thinning of the cortical layer, occurred in males and females in the 3X and 5X groups.

One control dog had a focal corneal opacity at necropsy.

Conclusions: This study supports the safe use of Otiserene® when administered at 1 mL per affected ear. Aural administration of Otiserene® to 4-month-old Beagles was associated with decreases in leukocytes, lymphocytes, and monocytes; decreased globulins; decreased fibrinogen and APTT; bilateral adrenal gland atrophy; decreased bone marrow cellularity; increased glycogen vacuolation; epidermal atrophy in external ear canals; and thymic atrophy. The observations were attributed to systemic exposure to dexamethasone in Otiserene®. One control dog had a focal corneal opacity at necropsy.

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 Otiserene®:

Not for use in humans. Keep this and all medications out of the reach of children. Humans with known hypersensitivity to any of the active ingredients in Otiserene® should not handle this product.

Avoid eye contact. If contact with eyes occurs, flush thoroughly with water for at least 15 minutes. If wearing contacts, rinse eyes first then remove contacts and continue to rinse. If irritation persists, contact a physician.

Avoid skin contact. In case of accidental skin contact, wash the area thoroughly with soap and water.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Otiserene®, 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

Otiserene®, as approved, 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)(i) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Otiserene®.

C. Patent Information

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