Date of Approval: 10/31/2011

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-330

EASOTIC

(hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate)
Otic suspension

For the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*)

Sponsored by:

Virbac AH, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-330
B. Sponsor:	Virbac AH, Inc. 3200 Meacham Blvd. Ft. Worth, TX 76137 Drug labeler code: 051311
C. Proprietary Name(s):	EASOTIC
D. Established Name(s):	Hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate
E. Pharmacological Category:	Topical anti-inflammatory, antifungal, and antibacterial otic
F. Dosage Form(s):	Otic suspension
G. Amount of Active Ingredient(s):	1.11 mg/mL hydrocortisone aceponate, 15.1 mg/mL miconazole nitrate, 1.5 mg/mL gentamicin sulfate
H. How Supplied:	It is available in a ten dose polyethylene canister with a soft applicator tip (canula) and a dose metered pump top
I. How Dispensed:	Rx
J. Dosage(s):	Verify that the tympanic membrane is intact. Carefully insert the canula into the affected external ear canal(s) and apply 1 mL (a single pump) once per day for 5 days. Wash hands after usage.
K. Route(s) of Administration:	Otic
L. Species/Class(es):	Dogs
M. Indication(s):	EASOTIC suspension is indicated for the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis)* and bacteria (*Staphylococcus pseudintermedius)*

II. EFFECTIVENESS:

A. Dosage Characterization:

Study Title and Number: *In vitro* determination of non-interference of gentamicin, miconazole, and hydrocortisone in combination against canine otitis externa pathogens, No. U-184.030000-30002.

Investigator: Don Bade, Fort Collins, CO

Purpose and Procedures: The objective of this laboratory study was to determine *in vitro* noninterference of combinations of gentamicin, miconazole, and hydrocortisone against bacterial and yeast isolates collected from clinical cases of canine otitis. Results of the *in vitro* noninterference assays demonstrated, in accordance with 21CFR 514.1(b)(8)(v), that each component made a contribution to the antimicrobial effect. Ten isolates each of *Staphylococcus pseudintermedius, Pseudomonas aeruginosa,* and *Malassezia pachydermatis* were arbitrarily selected from a pool of isolates from cases of canine otitis externa and were used to determine minimal inhibitory concentrations (MIC) for gentamicin, miconazole, and hydrocortisone. Fractional inhibitory concentration index (FICI) determinations were calculated from MICs obtained from a modified checkerboard evaluation of the various combinations.

Results: There was no activity of gentamicin (MICs > 32 µg/mL) or hydrocortisone (MICs > 22.4 µg/mL) against any *M. pachydermatis* isolates. Miconazole MICs ranged from 0.6-1.2 with an MIC50 and MIC90 of 0.6 µg/mL. There was no activity of miconazole (MICs > 80 µg/mL) or hydrocortisone (MICs > 22.4 µg/mL) against any *P. aeruginosa* isolates. Gentamicin MICs ranged from 1-8 with an MIC50 of 2 µg/mL and an MIC90 of 4 µg/mL. There was no activity of hydrocortisone (MICs > 22.4 µg/mL) against any *S. pseudintermedius* isolates. Gentamicin MICs ranged from 0.12-32 with an MIC50 and MIC90 of 0.25 µg/mL. Miconazole MICs ranged from 2.5-5 µg/mL with an MIC50 of 2.5 µg/mL and MIC90 of 5 µg/mL.

Except for the miconazole/hydrocortisone combination, all combinations against *P. aeruginosa* and *S. pseudintermedius* resulted in no effect on the MICs for 100% of the isolates, and resulted in an indifferent/autonomous FICI for all isolates. The miconazole/hydrocortisone combination was tested against *M. pachydermatis*, and resulted in no effect on the MICs, and an indifferent/autonomous FICI for all isolates. Other results for the combinations include:

- Gentamicin/Miconazole: Nine out of 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI, and one showed an apparent antagonism of one doubling dilution increase in the miconazole concentration. This isolate was different from the isolate described in the three-way test below.

- Gentamicin/Hydrocortisone: No effect on the MICs could be interpreted for *M. pachydermatis* since neither compound was active against these isolates.

- Miconazole/Hydrocortisone: Seven out of 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI, and three showed an apparent antagonism of only one doubling dilution increase in the miconazole concentration. Nine out of 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI, and one showed an antagonism of only one doubling dilution increase in the miconazole concentration.

- Gentamicin/Miconazole/Hydrocortisone: Nine out of 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI, and one showed an apparent antagonism of one doubling dilution increase in the miconazole concentration.

Conclusion: Results of *in vitro* tests to determine FICIs demonstrated a lack of interference between the 2 active ingredients. MICs indicate that gentamicin is active against *S. pseudintermedius* and *P. aeruginosa*, and miconazole is active against *M. pachydermatis*. Therefore, to ensure consistent effectiveness against the range of microorganisms (gram-negative and gram-positive bacteria, yeast, and fungi) commonly associated with canine otitis externa, both active ingredients are essential.

B. Substantial Evidence:

Clinical Efficacy and Safety Study Title: Field effectiveness and safety of 184.03 suspension (gentamicin sulfate, miconazole nitrate and hydrocortisone aceponate) for the treatment of otitis externa in dogs. U-184.030000-30004

Type of Study: This study was a double-masked, placebo-controlled effectiveness study conducted according to Good Clinical Practices.

Locations and Investigators: This study was conducted at eight veterinary clinics in the United States (Table 1).

Table 1: Investigators

Dr. Susan Baker Palm Beach, FL	Dr. Lynn Buzhardt Zachary, LA
Dr. Samuel Geller Quakertown, PA	Dr. Bradley Gray Chadds Ford, PA
Dr. David Lukof Harleysville, PA	Dr. Abraham Mathew Palm Beach Gardens, FL
Dr. Dean Rund Springfield, MO	Dr. Roger Sifferman Springfield, MO

General Study Design

Objective of the Study: The objective of the study was to determine the effectiveness and safety of EASOTIC for the treatment of *otitis externa*. Effectiveness was determined by improvement in the clinical score from baseline (visit 1) to the final assessment (visit 4). The safety analysis was based on the evaluation of clinical pathology parameters and the occurrence of adverse events during the study.

Test Animals: Two hundred and sixteen client-owned dogs were enrolled and included in the safety analysis. One hundred and forty-five were administered EASOTIC and 71 were administered a placebo control. Fifty-nine dogs were excluded from the effectiveness analysis, and 157 dogs were used to evaluate effectiveness; 104 were administered EASOTIC and 53 were administered the placebo control. The dogs enrolled ranged in age from 1 year, 2 months old to 15 years, 10 months old and ranged in weight from 5.1 to 171.9 lbs.

Control and Treatment Groups: Dogs were randomly assigned to either EASOTIC or to the placebo control. The placebo control was a non-vehicle solution containing glycerin and titanium dioxide.

Table 2: Treatment groups

Tx Group	Dose	Number and Gender of Animals
EASOTIC	1 mL once daily	72 F, 73 M
Placebo	1 mL once daily	35 F, 36 M

Inclusion Criteria:
To be enrolled in the study, a dog had to have a total clinical score of 4 or greater, with a score of 1 or more in at least 3 of the following six signs (rated 0 – 3):

- malodor from the ear
- discharge from the ear
- scratching at the ear (pruritis)
- redness (erythema) of the external ear canal
- swelling or hypertrophy of the external ear structures
- signs of pain or discomfort (reluctance to have ears handled)

Exclusion Criteria:

- less than 12 weeks of age
- pregnant or lactating
- known hypersensitivity to topical antibiotics, antifungals, or steroids
- received topical or oral antibiotics (including ear washes) within 60 days prior to enrollment
- received topical or oral antifungals (including ear washes) within 30 days prior to enrollment
- received oral or topical corticosteroids within 30 days prior to enrollment
- received injectable corticosteroids within 90 days prior to enrollment
- cranial neurologic signs
- parasitic skin or otic disease
- damage to the tympanum
- cutaneous manifestations of cancer or auto-immune disease
- stenotic or calcified ear canals indicative of refractory, chronic otitis
- diagnosed, but uncontrolled endocrinopathy
- severe co-existing metabolic, endocrine, or immune diseases

Drug Administration: A 1 mL dose of Easotic or placebo article was dispensed from the dose metered canister into the external ear canal of the affected ear(s) once per day for five consecutive days.

Variables Measured: Clinical score, ear cytology, microbial culture, and sensitivity.

Clinical Evaluation: All dogs that were determined to have bacterial and/or yeast otitis externa (based on a clinical score of 4 or greater and an otic cytology score of 2 or greater) were evaluated over the course of 30 days during four office visits on Day 1, Days 3-5, Days 12-15, and Days 26-30. Clinical pathology was performed at visit 1, visit 4, and/or withdrawal.

Dogs with bilateral otitis were included in the study. In these cases, the Investigators were instructed to treat both ears but only the right ear was evaluated throughout the study.

A clinical score was calculated for each dog at each visit by totaling the scores for each individual clinical sign. The six clinical signs evaluated in this study were: malodor, aural discharge, pruritis, erythema, swelling, and pain. The individual clinical scores were assigned based on the severity of that sign (0=absent; 1=mild; 2=moderate; 3=severe). Dogs with a clinical score of 4 or greater (out of a possible 18) were eligible to be enrolled. An ear swab was collected at visits 1 and 3 to help evaluate response to therapy and the cytology score was based on the number of bacteria and yeast from the swab.

Samples were collected at visit 1 from the external ear canal of affected ears and cultured for the presence and quantification of *S. pseudintermedius*, *P. aeruginosa*, and *M. pachydermatis*. Isolates were tested for their susceptibility to gentamicin or miconazole, as appropriate.

Criteria for Success/Failure: The criteria for treatment success was a clinical score of 2 or below at the visit 4, with no single clinical score getting worse at visit 4.

Statistical Analysis: The primary analysis for effectiveness was a comparison of the proportions of treatment success in each group using a generalized linear mixed model. The statistical model included group as a fixed effect and site and the site by group interaction as random effects, and assumed a binomial distribution with logit link. The difference between treatment groups was evaluated at a 2-sided α=0.05.

Clinical pathology variables with continuous values were analyzed using mixed models with baseline value as covariate, treatment as fixed effect and site and site by treatment interaction as random effects. The difference between treatment groups was evaluated at a 2-sided α=0.10.

Results: The effectiveness analysis included 104 dogs in the EASOTIC group and 53 dogs in the control group. There were 68 successfully treated cases and 36 failures in the EASOTIC group, and 14 successes and 39 failures in the control group. Table 3 summarizes the results of the statistical analysis, showing that the proportions of success in the two groups are significantly different (P-value=0.0179). Based on the analysis, the estimated success rate in EASOTIC-

treated dogs is 68.5%, higher than the estimated success rate of 21.8% in the control group.

Table 3: Summary of the primary statistical analysis of the proportion of treatment successes in each group

Treatment Group	Number of Dogs	Percent Success[a]	95% Confidence Interval[a]
EASOTIC	104	68.5	(44.3, 85.6)
Control	53	21.8	(7.6, 48.5)
P-value		0.0179	

[a] Estimated percent success and confidence intervals were back-transformed from the generalized linear mixed model (GLMM) least squares estimates.

Safety Analysis: There were no clinically significant drug-related findings in hematology or serum chemistries.

Microbiology: Administration of EASOTIC was shown to be effective at treating cases of otitis externa caused by *S. pseudintermedius* (37 successful cases and 15 failures) and *M. pachydermatis* (59 successful cases and 34 failures) (Table 4). Only these species were isolated from ≥10 cases successfully treated with EASOTIC. *P. aeruginosa* was isolated at visit 1 in 2 successful cases and 3 failures. Susceptibility data (MIC ranges and MIC50 values) for *S. pseudintermedius* and *M. pachydermatis* isolates obtained at visit 1 and withdrawal did not show any correlation between higher MICs and treatment failure. This was shown whether data was analyzed across the population or by individual case/animal.

Table 4. Summary of all antimicrobial susceptibility data from 157 evaluable cases included in the Effectiveness database upon entry at Visit 1 (V1) and at withdrawal (WD)

Treatment	CVM Conclusion	Sample	MIC Range (µg/mL) [MIC_{50}*]					
			n	***P. aeruginosa***	n	***S. pseudintermedius***	n	***M. pachydermatis***
EASOTIC	Success	V1	2	2	37	0.06-16 [0.12]	59	≤0.03-1 [0.12]
	Failure	V1	3	1-4 [2]	15	0.06-1 [0.12]	34	≤0.03-1 [0.12]
		WD	2	2-8	10	0.06-8 [0.12]	11	≤0.03-0.5 [0.25]
Control	Success	V1	1	2	5	0.12-32 [0.25]	11	≤0.03-2 [0.12]
	Failure	V1	-	-	20	0.06-16 [0.12]	36	≤0.03-0.5 [0.25]
		WD	1	1	15	0.06-16 [0.12]	22	≤0.03-0.5 [0.25]

* if calculable, MIC_{50} reflects the gentamicin (*P. aeruginosa* and *S. pseudintermedius*) or miconazole (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: Compared to the placebo, EASOTIC was safe and effective in treating otitis externa associated with *M. pachydermatis* and *S. pseudintermedius.*

III. TARGET ANIMAL SAFETY:

A. Target Animal Safety Study

Study Title and Number: Target Animal Safety Study of 184.03 Suspension (Gentamicin Sulfate, Miconazole Nitrate and Hydrocortisone Aceponate) when Administered Aurally in 12 Week Old Beagle dogs. #U-184.030000-30003/KFI-021-SC-0909.

Type of Study: Laboratory safety study (GLP)

Study Director: Jonathan Hare, DVM, PhD.
Stouffville, Ontario, Canada

General Design:

Test Animals: A total of 32 twelve-week old Beagle dogs were used in this study. Twenty-four dogs (12 male and 12 female) were administered EASOTIC and 8 dogs (4 male and 4 female) were used as a control.

Dosage form: Final market formulation of EASOTIC containing miconazole nitrate (15.1 mg/mL), gentamicin sulfate (1.5 mg/mL), and hydrocortisone aceponate (1.11 mg/mL) was used. The control was a non-vehicle placebo (glycerin with titanium dioxide).

Route of administration: Aural

Dosages used: Treatment groups are shown in Table 5.

Table 5. Dose Groups

Group	Treatment	Dosage of Active Ingredient	Regimen	No. Dogs
T0	Control	0X (5 mL/ear/day)	5 mL/ear/day administered as 1 mL every 2 hours for 8 hours daily for 15 days	4 males 4 females
T1	Active	1X (1 mL/ear/day)	1 mL/ear/day administered once daily for 15 days	4 males 4 females
T3	Active	3X (3 mL/ear/day)	3 mL/ear/day administered as 1 mL every 2 hours for 4 hours daily for 15 days	4 males 4 females
T5	Active	5X (5 mL/ear/day)	5 mL/ear/day administered as 1 mL every 2 hours for 8 hours daily for 15 days	4 males 4 females

Test duration: Fifteen days

Clinical parameters evaluated: Veterinary clinical observations, general daily observations, temperature, feed consumption, behavior, ear assessments and hearing assessments, hematology, serum chemistry, urinalysis including urine sediment, fecal assessment, occult fecal blood, ACTH stimulation, and body weight.

Statistical Analysis: Continuous outcomes measured once during the study were analyzed by analysis of variance with treatment, sex, and treatment-by-sex interaction as fixed effects and cohort as a random effect. Continuous outcomes measured more than once were analyzed using repeated measures analysis of covariance with the above fixed and random effects and additionally day, sex-by-day, treatment-by-day, and treatment-by-sex-by-day as fixed effects.

Results:

a. Clinical observations: There were no treatment-related clinical effects on body weight, behavior, or temperature. There was a statistically significant treatment effect on food consumption ($p=0.0391$). The food consumption in the 3X and 5X groups was numerically higher than the control and 1X groups.

b. Dosing site observations: Papules and erythema of the inner pinnae and external ear canal were noted in all groups, including the controls. Ulceration of the inner pinnae and external ear canal was noted in the 1X and 5X dogs. The most common finding was mild to moderate aural erythema. While mild erythema was seen in all groups, moderate erythema was more prevalent in dogs administered EASOTIC. Severe aural erythema was seen only in one 3X dog. Mild aural swelling was noted in the control, 3X and 5X dogs.

c. Clinical Chemistry: There was a statistically significant treatment-by-day effect for alanine aminotransferase (p= 0.0010). One 5X dog on Day 15, and a second 5X dog on Days 10 and 15 had levels above the reference range.

There was a statistically significant treatment-by-day effect for alkaline phosphatase (ALP: p=0.0033). On Days 5, 10, and 15, the ALP values were higher in the 3X and 5X dogs as compared to the control dogs and also in the 1X dogs on Day 15.

There was a statistically significant treatment-by-day effect (p= 0.0053) for cholesterol. Two 1X dogs on Day 15, four 3X dogs on Days 5, 10, and 15, and one 5X dog on Day 5 had levels above the reference range. None of the control dogs had elevated cholesterol levels.

There was a statistically significant treatment effect (p=0.0093) for urea with a mild increase outside the reference range for one 1X dog and three 3X dogs. However, creatinine values and urine specific gravity levels remained within the reference range for all four dogs.

There was a statistically significant treatment effect ($p<0.0001$) for albumin, and total protein elevations above the reference range were seen in two 1X dogs, four 3X dogs, and two 5X dogs; all of these dogs exhibited elevated serum albumin levels. Normal total protein levels but elevated serum albumin levels above the reference range were seen in two 1X dogs, six 3X dogs, and six 5X dogs. Clinically significant elevations in either serum albumin or total protein levels were not seen in the control group.

Hematology: There were no treatment-related abnormal hematology values.

d. Plasma drug analysis: Bioanalysis of plasma for the active ingredients confirmed a dose response. Although no hydrocortisone aceponate (HCA), miconazole, or gentamicin concentrations were observed in the background (predose) blood samples, the concentrations of miconazole and gentamicin in some control animals were equal to or exceeded that observed in several of the dogs in the 1X dose group. In the 1X, 3X, and 5X treatment groups, concentrations of HCA, gentamicin, and miconazole were quantifiable in the plasma of most dogs, i.e. above the Limit of Quantification (LOQ). The LOQs of the analytical method were 1.0 ng/mL for HCA, 2.0 ng/mL for gentamicin, and 0.434 ng/mL for miconazole. The average accumulation of miconazole in the plasma over the 14 days of dosing in 1X, 3X, and 5X dogs were 4.1, 2.3, and 5.7, respectively, i.e. steady state plasma concentrations were approximately 2-6 X higher than observed after a single dose regardless of the amount of dose administered. The corresponding accumulation for gentamicin was 8.3, 8.8, and 9.2 for 1X, 3X, and 5X dogs, respectively. Only minimum accumulation was observed for HCA, and this was primarily associated with the 5X dosing group.

e. ACTH Stimulation: The main effect of treatment was statistically significant for pre-ACTH ($p=0.0002$) and post-ACTH ($p<0.0001$) levels. Each of the treated groups had significantly different and numerically lower cortisol values pre-ACTH as compared to the control group. These changes are considered related to the suppression of the hypothalamic-pituitary-adrenal axis seen with administration of exogenous corticosteroids.

f. Gross Pathology: Otitis externa, characterized by focal areas of superficial neutrophilic inflammatory responses in the external ear canal, was seen in three 3X dogs and three 5X dogs. These changes were graded as "mild" for all three 3X dogs. One 5X dog had "minimal" changes, while another had "mild" changes. The third 5X dog had "moderate" changes.

   The main treatment effect for liver weight to body weight ratio was statistically significant ($p=0.0016$) and numerically higher in the 3X and 5X dogs.

g. Histopathology: Most animals in all groups administered EASOTIC (eight 1X dogs, eight 3X dogs, and five 5X dogs) had hyperplastic changes in the external ear canal. These changes were not seen in any of the control animals. Histologically these changes were characterized as epidermal thickening with hyperkeratosis, acanthosis, and the accumulation of a more compact cornified layer of the dermis.

   Two 5X dogs with otitis externa had unilateral suppurative otitis media, characterized by an accumulation of proteinaceous exudate containing neutrophils in the cavity of the middle ear. One dog had a "marked" otitis media infection along with suppurative otitis externa in the same ear.

   Renal tubular crystals in the cortex and medulla were seen across all groups, as three control dogs, six 1X dogs, six 3X dogs, and seven 5X dogs were noted to have this lesion. All three of the control dogs had measurable levels of gentamicin. One 1X dog and three 3X dogs with tubular crystals also had mildly elevated BUN levels above the reference range. However, all four dogs demonstrated urine specific gravity and creatinine levels within the reference range.

   One 5X dog demonstrated minimal renal tubular basophilia and atrophy of the cortex. This dog also had tubular crystals in the medulla.

Conclusions: Aural administration of EASOTIC to 12 week old Beagle dogs at 1, 3, and 5 times the recommended dose (1 mL/ear/day) for 15 days (three times the treatment length) was associated with alterations of the hypothalamic-pituitary-adrenal axis as evidenced by the ACTH stimulation results. Other findings considered to be related to treatment include the development of aural hyperemia; the presence of renal tubular crystals and possibly renal tubular basophilia and atrophy; elevated liver weights; the development of otitis externa and media; and elevations in alanine aminotransferase, alkaline phosphatase, total protein, albumin, and cholesterol levels.

B. Other Safety Observations:

In foreign post-market pharmacovigilance data for EASOTIC collected from 16 different countries in Europe between the years 2008 and 2010 by Virbac S.A., there were approximately 0.006% suspected adverse reactions. The most commonly reported adverse reactions were transient hearing loss and application site erythema.

IV. HUMAN FOOD 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, CVM 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 EASOTIC:

- Not for use in humans. Keep this and all drugs out of reach of children.
- In case of accidental skin contact, wash area thoroughly with water. Avoid contact with eyes.
- Owners with known or suspected hypersensitivity to aminoglycoside antibiotics, azole antifungals, or hydrocortisone should not handle this product.
- In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

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 EASOTIC, when used according to the label, is safe and effective for the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*)

A. Marketing Status:

This product may be dispensed only by or on the lawful 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:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.