Date of Approval: September 20, 2015

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-440

CLARO

Florfenicol, terbinafine, mometasone furoate otic solution

Dog

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

Sponsored by:

Bayer HealthCare LLC, Animal Health Division

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I. GENERAL INFORMATION:

A. File Number

NADA 141440

B. Sponsor

Bayer healthCare LLC
Animal Health Division
12809 Shawnee Mission Pkwy.
Shawnee Mission, KS 66216

Drug Labeler Code: 000859

C. Proprietary Name

CLARO

D. Product Established Name

Florfenicol, terbinafine, mometasone furoate otic solution

E. Pharmacological Category

Topical antibacterial, antifungal, and anti-inflammatory

F. Dosage Form

Solution

G. Amount of Active Ingredient

16.6 mg/mL florfenicol, 14.8 mg/mL terbinafine (equivalent to 16.6 mg/mL terbinafine hydrochloride), 2.2 mg/mL mometasone furoate

H. How Supplied

CLARO is available in a single dose pre-filled laminate dropperette with a tapered tip; supplied in cartons containing 2, 10, or 20 dropperettes.

I. Dispensing Status

Rx

J. Dosage Regimen

Administer one dose (1 dropperette) per affected ear.

K. Route of Administration

Otic

L. Species/Class

Dogs

M. Indication

CLARO 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:

A dose of 1 tube (1 mL) administered to the external ear canal(s) once was selected for the treatment of otitis externa in dogs based upon Study P12-0026, which was a non-randomized, non-masked, non-placebo controlled exploratory study, conducted in 40 client-owned dogs with otitis externa to evaluate the effectiveness of a single dose of Formulation OE-006 (16.6 mg/mL florfenicol, 14.8 mg/mL terbinafine, and 2.2 mg/mL mometasone furoate). On Day 0, the dogs had to have an otitis clinical score of $\geq$ 6 (out of 4 parameters scored 0-3) in at least one ear for inclusion. The ear was cleaned with saline and treated with a single dose of 1.0 mL OE-006. An ear swab was collected on Day 0 for both microbiology and cytology, and an additional swab was collected for microbiology from dogs defined as treatment failures. The dogs' ear was evaluated on Days 14 (± 2) and 35 (± 2) to assess effectiveness. The definition of success was an otitis clinical score of ≤3 on Day 35 with no increase in the clinical score on any visit. The success of a single dose of OE-006 to treat otitis externa in dogs in this study was 89.5%.

B. Substantial Evidence

1. Non-Interference Study

   a. Study Title and Number: *In vitro* determination of non-interference of florfenicol, terbinafine and mometasone in combination against canine otitis externa pathogens, Study Number MR1306

   b. Investigator: Microbial Research Inc., Fort Collins, CO

      Purpose and Procedures: The objective of this laboratory study was to determine *in vitro* non-interference of combinations of florfenicol, terbinafine, and mometasone against bacterial and yeast isolates collected from clinical cases of canine otitis. Ten isolates of *Staphylococcus pseudintermedius, Escherichia coli, 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 florfenicol, terbinafine, and mometasone. Fractional inhibitory concentration index (FICI) determinations were calculated from MICs obtained from a modified checkerboard evaluation of the various combinations.

c. Results: There was little to no activity of florfenicol (MICs ≥ 64 µg/mL) and no activity of mometasone (MICs > 16 µg/mL) against any *M. pachydermatis* isolates. Terbinafine MICs ranged from 0.008-0.06 µg/mL with an MIC50 of 0.03 µg/mL and an MIC90 of 0.06 µg/mL. There was no activity of terbinafine (MICs > 8 µg/mL) or mometasone (MICs > 16 µg/mL) against any *E. coli* isolates. Florfenicol MICs ranged from 4-32 µg/mL with an MIC50 of 16 µg/mL and an MIC90 of 32 µg/mL. There was no activity of mometasone (MICs > 16 µg/mL) or terbinafine (MICs > 8 µg/mL) against any *S. pseudintermedius* isolates. Florfenicol MICs ranged from 2-8 µg/mL with an MIC50 and MIC90 of 4 µg/mL.

When testing the various combinations of active ingredients, the MIC50 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, except for one *S. pseudintermedius* isolate. Results for the combinations include:

- terbinafine/florfenicol/mometasone: All 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI; 9 out of 10 *S. pseudintermedius* isolates showed an indifferent/autonomous FICI, and 1 showed an antagonistic FICI; and 7 out of 10 *E. coli* isolates showed an indifferent/autonomous FICI, and 3 showed an antagonistic FICI with a one doubling dilution increase in florfenicol MIC.

- terbinafine/florfenicol: All 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI; 8 out of 10 *S. pseudintermedius* isolates showed an indifferent/autonomous FICI, and 1 each showed an antagonistic and synergistic FICI; and 5 out of 10 *E. coli* isolates showed an indifferent/autonomous FICI, and 5 showed an antagonistic FICI by a one doubling dilution increase in the florfenicol MIC.

- florfenicol/mometasone: No effect on the MICs could be interpreted for *M. pachydermatis* since neither compound was active against these isolates. Eight out of 10 *S. pseudintermedius* isolates showed an indifferent/autonomous FICI, and 1 each showed an antagonistic and synergistic FICI; and 9 out of 10 *E. coli* isolates showed an indifferent/autonomous FICI, and 1 showed an antagonistic FICI.

- terbinafine/mometasone: All 10 *M. pachydermatis* isolates showed an indifferent/autonomous FICI. Due to inactivity of the active ingredients, only 3 out of 10 *S. pseudintermedius* isolates had FICI data interpreted, which showed all 3 had an indifferent/autonomous FICI. Due to inactivity of the active ingredients, the FICI for *E. coli* was unable to be interpreted.

d. Conclusion: Results of *in vitro* tests to determine FICIs demonstrated a lack of interference between the 2 microbiologically-active ingredients. MICs indicated that florfenicol is active against *S. pseudintermedius* and active against *E. coli,* and terbinafine is active against *M. pachydermatis.*

2. Field Study

   a. Title: Clinical Field Study of Combination Otic Formulation OE-006 in Dogs; Study number P13-004

   b. Locations and Investigators: This study was conducted at eight veterinary clinics in the United States.

   Investigators and Locations

Dr. Justin Bruening Seguin, TX	Dr. Scott Buzhardt Zachary, LA	Dr. Terry Clekis Bradenton, FL
Dr. Joseph Kinnarney Reidsville, NC	Dr. Kristi Lively Knoxville, TN	Dr. Lynn Roberts Rural Hall, NC
Dr. Roger Sifferman Springfield, MO	Dr. Phillip Waguespack Baton Rouge, LA	n/a

   c. General Study Design

      (1) Study Objective: The objective of the study was to evaluate the field safety and effectiveness of a single administration of CLARO over a minimum period of 30 days for the treatment of otitis externa in dogs. The safety analysis was based on the evaluation of clinical pathology parameters and the occurrence of adverse events during the study.

      (2) Study Animals: Two hundred and twenty-one client-owned dogs were enrolled and included in the safety analysis. One hundred and forty-six were administered CLARO and 75 were administered a vehicle control. One hundred and eighty-three dogs were included in the effectiveness analysis; 120 were administered CLARO and 63 were administered vehicle control. The dogs enrolled were 17 weeks to 16 years old and weighed 4.9 to 122.2 pounds.

(3) Treatment Groups: Dogs were randomly assigned to either receive CLARO or the vehicle control in a 2:1 ratio.

Table 1: Treatment Groups

Treatment Group	**Number (and gender) of Dogs Treated**	**Number of Dogs Evaluated for Effectiveness**
CLARO	146 (73 F, 73 M)	120
Vehicle control	75 (39 F, 36 M)	63

(4) Inclusion Criteria: A dog had to be at least 12 weeks of age, have an intact tympanic membrane, and have a minimum total clinical score of 6 based on the following signs of otitis externa: erythema, exudate, swelling and ulceration.

(5) Exclusion Criteria: Dogs that met any of the following exclusion criteria were not eligible for study enrollment:

- Total clinical score of less than 6
- Concurrent *Otodectes cynotis* infection
- Presence of otic foreign body
- Ruptured tympanic membrane
- Stenotic or calcified ear canals indicative of refractory, chronic otitis
- Evidence of a head tilt or cranial neurologic signs
- Poor general health, e.g., severe co-existing metabolic, endocrine, or immune disease
- Cutaneous manifestations of cancer or auto-immune disease
- Received topical or oral antifungals (including ear washes) within the previous 30 days
- Treatment with systemic or topical antimicrobials within the previous 17 days
- Treatment with long-acting antimicrobials, e.g., CONVENIA, within the previous 30 days
- Treatment with parenteral or topical antihistamines within the previous 17 days
- Treatment with parenteral or topical anti-inflammatories, including short-acting corticosteroids within the previous 17 days
- Treatment with parenteral or topical long-acting corticosteroids within previous 28 days
- Treatment with a depo form of corticosteroids within the last 4 months
- Known hypersensitivity to topical antibiotics, antifungals, or steroids
- Pregnant or lactating
- Dogs belonging to employees of study site

(6) Drug Administration: Bilateral application was allowed if both ears were affected but only the evaluable ear was scored throughout the study. The right ear was considered the evaluable ear; if the right ear did not

qualify, the left ear was considered evaluable. Prior to treatment administration on Day 0, the entire external ear canal was cleaned with saline in both treatment groups. CLARO or the vehicle control was administered by a veterinarian or veterinary technician on Day 0. The solution was instilled into the external ear canal, followed by massaging the base of the ear to ensure distribution.

(7) Clinical Evaluation: The primary clinical effectiveness endpoint was based on the total otitis externa score of the evaluable ear on Day 30 (actual day ranged from Day 30 to Day 33). A clinical score was calculated for each dog at each visit by totaling the scores for each individual clinical sign of erythema, exudate, swelling, and ulceration. The individual clinical scores were assigned based on the severity of that sign (0=none; 1=mild; 2=moderate; 3=severe).

Clinical scoring was conducted prior to the first treatment on Day 0 then on Days 7, 14, and 30. A total clinical score was calculated for each dog at each visit by totaling the scores for each individual clinical sign of the evaluable ear.

Ear swabs were collected from the evaluable ears at Day 0 and cultured for the presence and quantification of *S. pseudintermedius, M. pachydermatis, E. coli, P. mirabilis, P. aeruginosa,* and β-hemolytic *Streptococcus* species. An additional ear swab was obtained at study exit from cases with clinical failure. Isolates were tested for their susceptibility to florfenicol and terbinafine, as appropriate.

Clinical pathology (hematology, serum chemistry, and urinalysis) was performed on Day 0 and Day 30, or at withdrawal. The ability or inability to hear was recorded on Days 0 and 30. Clinic personnel clapped their hands together in a location out of the dog's sight and observed if the dog turned toward where the noise originated.

(8) Criteria for Success/Failure: Dogs with Day 30 final total clinical scores of 3 or less, as well as no single individual score getting worse, were considered treatment successes.

(9) 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 treatment as a fixed effect and site and treatment by site as random effects. The difference between treatment groups was evaluated at a 2-sided 0.05 level of significance.

Clinical pathology variables were evaluated using an analysis of covariance (ANCOVA) with the pre-treatment value used as a covariate. The model included terms for the effects *Treatment* and *Site*, as well as the interaction *Treatment by Site*. The model term S*ite* and the interaction T*reatment by Site* were treated as random effects in the model. The difference between treatment groups was evaluated at a 2-sided 0.05 level of significance.

d. Results: The effectiveness analysis included 120 dogs in the CLARO group and 63 dogs in the control group. There were 87 successfully treated cases and 33 failures in the CLARO group, and 7 successes and 56 failures in the control group. Table 2 summarizes the results of the statistical analysis, showing that the proportions of success in the two groups are significantly different (P-value=0.0001). Based on the analysis, the success rate in CLARO- treated dogs is 72.5%, which is higher than the success rate of 11.1% in the control group.

Table 2: Day 30 Effectiveness Summary

Treatment Group	**Success (Score ≤3)**	**Failure (Score >3)**	**Total**
CLARO	87 (72.5%)	33 (27.5%)	120
Vehicle Control	7 (11.1%)	56 (88.9%)	63

There were no clinically significant test article-related findings in the hematology, serum chemistry, or urinalysis results. There were also no adverse reactions directly attributable to administration of CLARO. None of the dogs completing the study through Day 30 lost their ability to hear.

Administration of CLARO was shown to be effective at treating cases of otitis externa caused by *S. pseudintermedius* (58 successful cases and 16 failures) and *M. pachydermatis* (85 successful cases and 23 failures) (Table 3). Susceptibility data (MIC ranges and MIC50 values) for *S. pseudintermedius* and *M. pachydermatis* isolates obtained on Day 0 and withdrawal did not show any correlation between higher MICs and treatment failure. This result was shown whether data was analyzed across the population or by individual case/animal.

Table 3: Susceptibility for Florfenicol or Terbinafine as MIC Range (µg/mL) [MIC_{50}*] of the isolates obtained from 187 evaluable otitis externa cases at Day 0 (D0) and at withdrawal (WD).

Trt	Outcome	Visit	N	EC	N	PM	N	PA	N	SP	N	ST	N	MP
CLARO	Success	D0	6	8-32 [8]	2	4-8	5	>64	58	2-8 [4]	6	2	85	0.008-0.25 [0.03]
CLARO	Failure	D0	4	4-16 [16]	1	4	7	64->64 [>64]	16	2-4 [4]	4	2	23	0.015-0.06 [0.03]
CLARO	n/a	WD	3	8-16 [16]	1	8	5	>64	9	4	4	2	5	0.008-0.06 [0.03]
Control	Success	D0	0	n/a	0	n/a	0	n/a	6	4	0	n/a	8	0.008-0.06 [0.03]
Control	Failure	D0	5	4-16 [8]	2	4-8	7	64->64 [>64]	26	4	10	2	47	0.008-0.25 [0.03]
Control	n/a	WD	4	4-16 [16]	2	4-8	7	>64	23	2-4 [4]	8	2	41	0.008-0.12 [0.03]

* If 10 or more isolates, MIC_{50} reflects the florfenicol (*E. coli, P. mirabilis, P. aeruginosa, S. pseudintermedius,* β-hemolytic streptococci species) or terbinafine (*M. pachydermatis)* concentration that inhibited at least 50% of the isolates being described.

EC = *E. coli*, PM = *P. mirabilis*, PA = *P. aeruginosa*, SP = *S. pseudintermedius*, ST = β-hemolytic *streptococci* species, MP = *M. pachydermatis*

e. Adverse Reactions: The following adverse events were reported during the course of the field study:

Table 4: Frequency of Adverse Events by Treatment

Adverse Event	**CLARO N = 146 dogs**	**Control N = 75 dogs**
Abnormal integument (erythema, pyoderma, flea allergy dermatitis, pruritus, lipoma, etc.)	6	1
Coughing, tracheobronchitis	2	1
Limping, arthritis	2	1
Red eyes, conjunctivitis,	2	0
Aural hematoma	1	0
Cervical pain	0	1
Diarrhea	1	0
Lethargy, acting sick	1	0
Sneezing	0	1
Trauma/accident	1	1
Tympanic membrane thickening	1	0
Urinary incontinence	1	0
Urinary tract infection	1	1

f. Conclusion: CLARO administered once at a dose of 1 mL per affected ear in dogs is effective for the treatment of otitis externa associated with yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*) infections.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study

1. Study Title: Target Animal Safety Study of CLARO (Florfenicol, Mometasone, and Terbinafine) When Administered Aurally Once Every Two Weeks in Dogs: Study Number P12-018/8273986

2. Type of Study: GLP Laboratory Safety Study

3. Study Director: Covance Laboratories, Inc.
Madison, Wisconsin

4. General Study Design:

   a. Purpose: The objective of this study was to evaluate the toxicity of CLARO when administered to juvenile dogs.

   b. Animals: Twenty-four Beagle dogs (12 male and 12 female), 12 weeks of age at enrollment, were administered CLARO and 8 dogs (4 male and 4 female) were administered a placebo control (saline).

c. Dosage Form: The test article was the final formulation of CLARO containing 16.6 mg/mL florfenicol, 14.8 mg/mL terbinafine (equivalent to 16.6 mg/mL terbinafine hydrochloride), and 2.2 mg/mL mometasone. The placebo control administered was 0.9% sterile saline.

d. Treatment Groups: The study included four treatment groups (control, 1X, 3X, and 5X) as shown in Table 5:

Table 5: Treatment Groups

Group	Number and Sex of Animals	Dose per ear (mL)	Total dose volume (mL)
Control (0X)	4 males, 4 females	5	10
1X	4 males, 4 females	1	2
3X	4 males, 4 females	3	6
5X	4 males, 4 females	5	10

e. Dosage amount, frequency, and duration: Dogs were administered control article (saline) at 5 mL/ear or CLARO at 1X, 3X, or 5X the recommended dose of 1 mL/ear (2 mL/dog). The dose was administered via instillation into both ear canals every 2 weeks on Study Days 1, 15, and 29. The control article was administered in a manner equivalent to the 5X test article dose level. In the 3X, 5X, and control groups the dose was administered in aliquots of 1 mL/ear (2 mL/animal) every 2 hours until the total assigned dose volume was achieved for that animal.

f. Variables Measured: Clinical observations included general daily observations, cage-side observations, detailed observations and unscheduled observations, aural and otoscopic assessments and hearing assessments, body weights, food consumption, hematology, serum chemistry, coagulation profile, urinalysis, adrenocorticotropic hormone (ACTH) stimulation, organ weights, gross pathology, and histopathology.

g. Statistical Analysis: End points measured once post-treatment that did not include a pre-treatment measurement were analyzed using an analysis of variance (ANOVA) with *Treatment*, *Sex*, and *Treatment x Sex* as fixed effects. End points measured multiple times post-treatment that included a pre-treatment measurement were analyzed using repeated measures analysis of covariance (RMANCOVA) with *Treatment*, *Time*, and *Sex*; the two-way interactions *Treatment x Time*, *Treatment x Sex*, and *Sex x Time*; the three-way interaction *Treatment x Time x Sex*; and a covariate all as fixed effects. Animal was identified as the subject in the repeated statement. The pre-treatment value closest to dosing was used as the covariate.

5. Results: All dogs survived to scheduled necropsy. No clinically relevant treatment-related findings were noted in body weight, weight gain, hearing tests, or food consumption. Dogs administered CLARO were found to have post-treatment ear wetness or clear aural exudate.

   There was an increased group mean absolute neutrophil count in males in the 5X group, and decreased absolute lymphocyte and eosinophil counts, and increased AST in dogs administered CLARO at all dose levels. There was an

increased group mean total protein, increased cholesterol, and a decreased inorganic phosphorus concentration in dogs in the 3X and 5X groups. There was a lower group mean creatinine concentration relative to control group dogs in the 5X group and decreased calcium concentration in females in the 5X group. These changes were within the normal reference range, and not associated with clinical findings.

There was dose-dependent suppression of the adrenal cortical response to ACTH-stimulation on both Days 2 and 30 of the dosing phase in all groups administered CLARO; this effect was more pronounced on Day 30 of the dosing phase. This was accompanied by lower group mean and individual adrenal gland weight and atrophy of the zona fasciculata/reticularis of the adrenal cortex. Higher group mean and individual animal liver/gall bladder weight parameters occurred with corresponding hepatocellular enlargement/cytoplasmic change. There was a decrease in thymus weight not associated with microscopic lymphoid depletion.

6. Conclusion: This study supports the safe use of CLARO at the recommended clinical dose of 1 mL per affected ear in dogs. There were no clinically relevant CLARO-related findings noted in body weight, weight gain, hearing tests, or food consumption. CLARO administration was associated with post-treatment ear wetness or clear aural exudate, increased absolute neutrophil count, decreased absolute lymphocyte and eosinophil counts, suppression of the adrenal cortical response to ACTH-stimulation, decreased adrenal weight and atrophy of the adrenal cortex, increased liver weight with hepatocellular enlargement/cytoplasmic change, and decreased thymus weight. Other potential treatment-related effects included mild changes to AST, total protein, inorganic phosphorus, creatinine, and calcium.

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, 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 CLARO:

Human Warnings are provided on the product label as follows: "Not for use in humans. Keep this and all drugs out of 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. Humans with known hypersensitivity to florfenicol, terbinafine hydrochloride, or mometasone furoate should not handle 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 CLARO, 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 the appropriate treatment.

B. Exclusivity

CLARO, 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 safety and effectiveness of CLARO.

C. Patent Information:

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

VII. Appendix 1

September 20, 2015 – Original Version

May 25, 2016:

- Sponsor name and address changed from "Piedmont Animal Health, 204 Muirs Chapel Rd., suite 200, Greensboro, NC 27410" to "Bayer HealthCare LLC, Animal Health Division, 12809 Shawnee Mission Pkwy., Shawnee, KS 66216".
- Drug Labeler Code changed from "058147" to "000859"
- Quantities of the active ingredients revised from "15.0 mg/mL florfenicol, 13.3 mg/mL terbinafine (equivalent to 15.0 mg/mL terbinafine hydrochloride) and 2.0 mg/mL mometasone furoate" to "16.6 mg/mL florfenicol, 14.8 mg/mL terbinafine (equivalent to 16.8 mg/mL terbinafine hydrochloride) and 2.2 mg/mL mometasone furoate" to account for the density of the solution.