Date of Approval: November 4, 2014

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-437

OSURNIA

florfenicol, terbinafine, betamethasone acetate

Otic gel

Dogs

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

Sponsored by:

Novartis Animal Health US, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-437

B. Sponsor

Novartis Animal Health US, Inc.,
3200 Northline Ave., suite 300
Greensboro, NC 27408

Drug Labeler Code: 058198

C. Proprietary Name

OSURNIA

D. Established Name

Florfenicol, terbinafine, betamethasone acetate

E. Pharmacological Category

Antibacterial, antifungal, and anti-inflammatory

F. Dosage Form

Otic gel

G. Amount of Active Ingredient

10 mg florfenicol, 10 mg terbinafine, and 1 mg betamethasone acetate per mL

H. How Supplied

It is available in a single use tube with a flexible soft tip, supplied in cartons containing 2 or 20 tubes.

I. Dispensing Status

Rx

J. Dosage Regimen

OSURNIA should be administered in the clinic. Clean and dry the external ear canal before administering the initial dose of the product. Administer one dose (1 tube) per affected ear(s) and repeat administration in 7 days. Do not clean the ear canal for 45 days after the initial administration to allow contact of the gel with the ear canal.

K. Route of Administration

Otic

L. Species

Dogs

M. Indication

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

II. EFFECTIVENESS

Note: Compound A-20114-B and OSURNIA are the same drug formulation.

A. Dosage Characterization

A dose of 1 tube (1 mL) administered to the external ear canal(s) twice, 7 days apart, was selected for the treatment of otitis externa in dogs based upon the following study:

1. Pilot Field Trial to Evaluate the Efficacy and Safety of Various Dose Regimens Using Compound A-20114-B for the Treatment of Canine Otitis Externa Complicated by Susceptible Strains of Bacteria and Yeast (Study 11-012, 2012).

   One hundred twenty-one dogs were enrolled in a double-masked, placebo controlled, multicenter pilot study to evaluate the safety and effectiveness of OSURNIA administered as either a single dose or two doses (7 days apart) for the treatment of canine otitis externa complicated by susceptible strains of bacteria and yeast. Dogs were enrolled in a 1:1:2:2 ratio to one of the four treatment groups: OSURNIA single administration, placebo control, OSURNIA twice administration, or active control, respectively.

   The primary clinical effectiveness evaluation was based on the total otitis externa score of the evaluable ear at each visit (Day 0, 7, 14, 30, and 45) using a standardized 12 point scoring system. A minimum score of ≥6 was required for enrollment on Day 0. A score of ≤2 was considered a clinical success. The dogs were assessed for pain, erythema, exudate, swelling, odor, and ulceration at each visit. Ninety-nine dogs were evaluated for effectiveness. *Malassezia pachydermatis* and *Staphylococcus pseudintermedius* were the most commonly isolated pathogens.

   On Day 45, the effectiveness of OSURNIA, administered twice, 7 days apart, was greater compared to: administration once, active control, and placebo. The study supported two doses of OSURNIA administered one week apart for the treatment of otitis externa.

2. Depletion of florfenicol, terbinafine, and betamethasone acetate in dog ears after intra-auricular administration of auricle otic gel (Study 12-020, 2012).

   An ear swab depletion study (CRA-12-020) was conducted in 33 dogs with normal ears to estimate the duration of activity of the three active ingredients in OSURNIA. Each ear on a dog was considered to be an independent observation and was sampled at a different time point. Only one sample could be collected from each ear, so a total of six ear swabs were collected at each time point. The ear swab samples were collected by inserting a cotton swab up to a standard depth in the ear canal. Samples were collected at 1.5 hours, and at days 1, 2, 4, 7 (just before the second administration), 8, 9, 11, 14, 24, and 35. In order to maximize the inferential value associated with the small samples size, prediction intervals (95% confidence intervals on predicted individual values) were generated. These intervals provided an estimate of the range of concentrations for each drug at 45 days after the initial dose, where day 45 was the final evaluation day in the field study to support substantial evidence of effectiveness. The prediction intervals suggest that there could be therapeutic concentrations of OSURNIA present at 45 days in dogs with normal ears. It is assumed that the depletion of the drug would be faster in ears affected with otitis externa due to increased absorption through the disrupted skin barrier and drug degradation secondary to inflammation.

B. Substantial Evidence

1. Non-Interference and Susceptibility Studies

   a. Title: *In vitro* determination of non-interference of florfenicol, terbinafine and betamethasone acetate in combination against canine otitis externa pathogens (Study 10-003, 2010).

   b. Investigator: Don Bade, Fort Collins, CO

   c. Study Design:

      (1) Objective: To determine *in vitro* non-interference of combinations of florfenicol, terbinafine, and betamethasone acetate against bacterial and yeast isolates collected from clinical cases of canine otitis externa.

      (2) Procedures: Between 24 to 30 isolates each of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus pseudintermedius,* and *Malassezia pachydermatis* were arbitrarily selected from a pool of isolates obtained from cases of canine otitis externa. Samples were received from at least 3 different geographical locations within the USA. These isolates were used to determine minimum inhibitory concentrations (MIC) for florfenicol (FFN), terbinafine (TRB), and betamethasone acetate (BTM). Fractional Inhibitory Concentration Index (FICI) determinations were calculated from MICs obtained from a modified checkerboard evaluation of the following combinations: TRB/FFN, FFN/BTM, TRB/BTM, and TRB/FFN/BTM. Several ratios of each combination were additionally tested.

d. Results: There was no activity of florfenicol or betamethasone acetate against *M*. *pachydermatis* isolates. The terbinafine MIC for *M. pachydermatis* ranged from 0.008-0.12 mcg/mL (MIC50/90 of 0.03/0.12 mcg/mL, respectively). There was no activity of terbinafine or betamethasone acetate against *P. aeruginosa*, *E. coli*, or *S. pseudintermedius* isolates. The florfenicol MIC for *P. aeruginosa* ranged from 32- to >128 mcg/mL (MIC50/90 of >128/>128 mcg/mL, respectively). The florfenicol MIC for *E. coli* ranged from 1-16 mcg/mL (MIC50/90 of 8/16 mcg/mL, respectively), and for *S. pseudintermedius* it ranged from 1-4 mcg/mL (MIC50/90 of 2/4 mcg/mL, respectively).

- TRB/FFN combination: This combination showed indifferent/autonomous FICI for the majority of the isolates. One *E. coli* and one *P. aeruginosa* isolate each showed antagonism for some of the tested ratios. Considering the various tested ratios, 19-31% of the *M. pachydermatis* isolates and occasional *S. pseudintermedius* isolates indicated synergy at each of the tested ratios.

- FFN/BTM combination: This combination showed indifferent/autonomous FICI for 100% of the *E. coli* and *P. aeruginosa* isolates. One *S. pseudintermedius* isolate showed synergism for both tested ratios. No effect on the MICs could be interpreted for *M. pachydermatis* because neither compound was active against these isolates.

- TRB/BTM combination: This combination showed indifferent/autonomous FICI for the majority of the *M. pachydermatis* isolates. Twenty seven percent of the *M. pachydermatis* isolates indicated synergy at each of the tested ratios. No effect on the MICs could be interpreted for *E. coli, P. aeruginosa,* and *S. pseudintermedius* because neither compound was active against these isolates.

- TRB/FFN/BTM combination: This combination showed indifferent/autonomous FICI for the majority of the isolates. One *E. coli* isolate showed antagonism for one of the tested ratios. Approximately 23-27% of the *M. pachydermatis* isolates and occasional *P. aeruginosa* and *S. pseudintermedius* isolates indicated synergy at each of the tested ratios.

e. Conclusion: Results of *in vitro* tests to determine FICIs demonstrated a lack of interference between the three active ingredients in OSURNIA. The MICs indicated that *S. pseudintermedius* and *E. coli* were susceptible to florfenicol and *M. pachydermatis* was susceptible to terbinafine.

2. Field Effectiveness Study:

a. Title: Field Trial to Evaluate the Efficacy and Safety of Two Doses of Compound A-20114-B Administered One Week Apart for the Treatment of Canine Otitis Externa Complicated by Susceptible Strains of Bacteria and Yeast (Study 12-001).

b. Investigators: The study was conducted at fifteen veterinary clinics located in various areas of the United States as listed below.

Dr. Jay Butan, Lake Worth, FL
Dr. Kimberly Fanning, Charlotte, NC
Dr. Chris Konvalinka, Bahama, NC
Dr. Ronald Buzhardt, Zachary, LA
Dr. Barry Fly, Nolensville, TN
Dr. Mark Marks, Lawrence, KS
Dr. Beth Carroll, Durham, NC
Dr. Samuel Geller, Quakertown, PA
Dr. Roger Sifferman, Springfield, MO
Dr. Terry Clark, Irving, TX
Dr. Amy Jessup, Winston-Salem, NC
Dr. Mitch Spindell, Clemmons, NC
Dr. Shane Daigle, Cedar Park, TX
Dr. Edward Jezbera, Riverside, CA
Dr. Philip VanVranken, Battle Creek, MI

c. Study Design: This was a randomized, double-masked, placebo (vehicle)-controlled, multi-center field study.

(1) Objective: To evaluate the field safety and effectiveness of two doses of OSURNIA administered one week apart in comparison with a placebo control administered at the same interval for the treatment of canine otitis externa complicated by susceptible strains of yeast and bacteria.

(2) Study Animals: The study enrolled 284 client-owned dogs of 49 different breeds, 4 months to 16.4 years of age, and 3.7 lbs. to 178 lbs. body weight. A total of 36.9% of dogs had a subchronic presentation of otitis externa, while 36.2% had chronic and 26.8% had acute presentations. Most dogs (91.5%) presented with bilateral otitis externa.

(3) Treatment Groups: The dogs were randomized in a 2:1 ratio to the OSURNIA or the placebo control groups, respectively. Table 1 details the number of dogs enrolled and evaluated for effectiveness in each treatment group. All dogs were evaluated for safety.

Table 1: Number of Dogs in Each Treatment Group

Treatment Group	OSURNIA	Placebo control (vehicle)
Number (and gender) of Dogs Treated	190 (90F, 100M)	94 (52F, 42M)
Number of Dogs Evaluated for Effectiveness	159	76

(4) Inclusion/exclusion criteria: The following inclusion criteria were met prior to study enrollment: Informed Consent Form signed, minimum age of 8 weeks, minimum total clinical score of 6, and intact tympanic membranes for all ears which received treatment.

Dogs that met any of the following exclusion criteria were not eligible for study enrollment:

- treatment with systemic, topical, or otic antimicrobials, including antifungals, within the last 14 days (including medicated shampoos);
- treatment with anti-inflammatories, including short-acting corticosteroids within the last 14 days;
- treatment with long-acting corticosteroids within the last 28 days;
- treatment with cyclosporine within the last 14 days;
- treatment with any otic cleaner within the last 7 days;
- treatment with anti-histamine within the last 14 days;
- treatment with an analgesic agent within the last 7 days (may have been used as part of the sedation protocol if required to evaluate the dog's ear);
- suspected or confirmed endocrine disorder (i.e. diabetes mellitus, hypo or hyper thyroid disease, etc.);
- concurrent *Otodectes cynotis* infections;
- presence of otic foreign body;
- dogs with known or suspected hypersensitivity to florfenicol, terbinafine, or betamethasone acetate;
- dogs intended for breeding, or pregnant or lactating; or
- staff-owned pets and pets enrolled in other clinical studies.

(5) 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 ear canal was cleaned with saline in both treatment groups. Ears were not cleaned or flushed at any time during the study after the initial administration of treatment on Day 0. OSURNIA or the placebo control was administered by the dispenser on Days 0 and 7. The gel was applied topically to the ear canal, followed by massaging the base of the ear to ensure distribution of the formulation.

(6) Measurements and Observations: The primary clinical effectiveness endpoint was based on the total otitis externa score of the evaluable ear on Day 45 using a 12 point score system [Pain (0-2); Erythema (0-2); Exudate (0-2); Swelling (0-2); Odor (0-2); Ulceration (0-2)]. Clinical scoring was conducted prior to the first treatment on Day 0 then on Days 7 (prior to the second treatment administration), 14, 30, and 45. 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. A minimum total clinical score of ≥6 on Day 0 was required for enrollment on the study.

Ear swabs were collected from the evaluable ears at Day 0 and cultured for the presence of bacteria and yeast. 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.

(7) Definition of Success/Failure: Each case was considered a success if it completed the study and the total score on Day 45 was ≤ 2. A case was considered a failure if it scored greater than a 2 or was removed from the study prior to Day 45.

(8) Statistical Analysis: The clinical outcome for each case (success or failure) was analyzed using a generalized linear mixed model with logit link. The model included the fixed effect 'treatment' and random effects 'site' and the interaction 'treatment-by-site'.

d. Results: Two hundred and thirty-five (235) cases (159 OSURNIA and 76 placebo) were included in the effectiveness evaluation. The OSURNIA group was statistically significantly different (p=0.0094) from the placebo group with clinical success rates of 64.78% and 43.42%, respectively. The table below summarizes the observed frequency of successes and failures by treatment group.

Table 2: Day 45 Effectiveness Summary

Treatment Group	Success (Score ≤ 2)	Failure (Score > 2)	Total
OSURNIA	103	56	159
Placebo Control	33	43	76
Total	136	99	235

Malassezia pachydermatis and *Staphylococcus pseudintermedius* were the most commonly isolated pathogens in the ear culture at study initiation. The terbinafine MIC_{50} against *M. pachydermatis* was 0.03 mcg/mL and the florfenicol MIC_{50} against *S. pseudintermedius* was 4 mcg/mL. There were no significant changes in susceptibility between pre- and post- treatment samples. There were at least 10 isolates from successfully treated cases of *M. pachydermatis, S. pseudintermedius,* and *P. aeruginosa*. However, there were only three dogs with a predominant *P. aeruginosa* culture and they were all treatment failures. Therefore, it was concluded that OSURNIA may not be effective in treating otitis externa in which *P. aeruginosa* is the only pathogen present. See table 3a for treatment with OSURNIA and table 3b for placebo control group.

Table 3a: Susceptibility for Florfenicol or Terbinafine as MIC Range (µg/mL) [MIC50[1]] of the isolates obtained from 159 evaluable canine otitis externa OSURNIA-treated cases at Visit 1 (Day 0) and at withdrawal.

OSURNIA Clinical Results	Sample[2]	*n*	*E. coli*	*n*	*P. mirabilis*	*n*	*P. aeruginosa*	*n*	*Staph. pseud.*	*n*	β-*hemolytic Strep.* spp.	*n*	*M. pachy.*
Successes	D0	1	8	4	4-8 [8]	10	>64	51	2-8 [4]	5	2	89	≤0.004-0.12 [0.03]
Failures	D0	5	4-16 [16]	4	4-8 [8]	13	>64	29	2-4 [4]	15	2-4 [2]	36	≤0.004-0.25 [0.015]
-	Withdrawal	6	4-16 [16]	3	8	14	>64	19	2-4 [4]	12	2-4 [2]	23	≤0.004-0.25 [0.015]

[1] If calculable, MIC50 reflects the florfenicol (bacteria) or terbinafine (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described.
[2] Pathogens (n) cultured on Day 0 may not be the same pathogens cultured at withdrawal.

Table 3b: Susceptibility for Florfenicol or Terbinafine as MIC Range (µg/mL) [MIC50[1]] of the isolates obtained from 76 evaluable canine otitis externa placebo-treated cases at Visit 1 (Day 0) and at withdrawal

Placebo Control Clinical Result	Sample[2]	*n*	*E. coli*	*n*	*P. mirabilis*	*n*	*P. aeruginosa*	*n*	*Staph. pseud.*	*n*	β-*hemolytic Strep.* spp.	*n*	*M. pachy.*
Successes	D0	2	16	0	-	1	>64	15	2-4 [4]	2	2	24	≤0.004-0.12 [0.015]
Failures	D0	5	8-16 [16]	2	4-8	5	>64	22	2-4 [4]	5	2	37	≤0.004-0.06 [0.015]
-	Withdrawal	3	4-16	3	8	6	>64	18	2-4 [4]	8	2	33	≤0.004-0.12 [0.015]

[1] If calculable, MIC50 reflects the florfenicol (bacteria) or terbinafine (*M. pachydermatis*) concentration that inhibited at least 50% of the isolates being described.
[2] Pathogens (n) cultured on Day 0 may not be the same pathogens cultured at withdrawal.

e. Adverse Reactions:

The following adverse reactions were reported during the course of the field study:

Table 4: Frequency of Adverse Reaction by Treatment

Adverse Reaction	OSURNIA (n=190)	Placebo (n=94)
Elevated Alkaline Phosphatase	15 (7.9%)	3 (3.2%)
Vomiting	7 (3.7%)	1 (1.1%)
Elevated AST, ALT, ALP*	2 (1.1%)	0 (0.0%)
Weight loss (>10% body weight)	1 (0.53%)	0 (0.0%)
Hearing Decrease/Loss	1 (0.53%)	1 (1.1%)

*Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP). Two dogs with pre-existing elevations in ALP were reported to have an increase in liver enzymes (ALP, ALT and/ or AST) at study exit. Subsequent clinical chemistries returned to pre-treatment levels in one dog, while no follow up was performed for the second dog.

f. Conclusion: OSURNIA administered twice, one week apart, at a dose of 1 mL per affected ear in dogs is effective for the treatment of otitis externa associated with bacteria (*Staphylococcus pseudintermedius*) and yeast (*Malassezia pachydermatis*) infections. The adverse reactions in dogs treated with OSURNIA included vomiting, mild elevations in liver enzymes (ALT, AST, and/or ALP), and decreased hearing.

III. TARGET ANIMAL SAFETY

A. Study Title and Number: Formulation A-20114B: A Five-Week Intra-auricular Target Animal Safety Study in Mongrels.

1. Study Location: AVANZA Laboratories
Gaithersburg, Maryland, USA

2. General Design:

a. Purpose: This study evaluated the safety of OSURNIA in mixed breed hounds. Local absorption of the three active substances was assessed.

b. Description of Test Animals: Twenty four healthy mixed breed hound dogs, approximately 4 months old at first dose administration, weighing 10-14 kg.

c. Treatment and Control Groups: The dogs were randomly assigned to treatment groups as shown in Table 5:

Table 5: Control and Treatment Groups

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

*Control: Saline -0.9% sodium chloride for injection, USP

d. Dosage form: OSURNIA otic gel.

e. Route of administration: Otic application, into the ear canal.

f. Dosage amount, frequency, and duration: Dogs were administered control article (saline) or OSURNIA at 1X or 5X the recommended dose via instillation into both ear canals on Study Day (SD) 1, 8, 15, 22, 29, and 36. The 1X recommended dose was 1 mL/ear or 2 mL/dog with repeated administration in 7 days and the 5X dose was 5 mL/ear or 10 mL/dog with repeated administration in 7 days. In the control (0X) and 5X group, the dose was administered at least 1 mL per ear approximately every 2 hours until the entire dose had been administered. The base of the ear was massaged after dose administration. Total study duration was 37 days.

g. Variables measured: The following variables were measured prior to initiation of the study, during, and/or at the end of the study: clinical observations, veterinary physical examinations, hearing tests, body temperature, pulse and respiration rates, body condition scores, body weights, food consumption, adrenocorticotropic hormone (ACTH) stimulation tests, hematology, clinical chemistries, coagulation, urinalyses, organ weights, gross pathology and histopathology (all tissues in 0X and 5X groups; and on gross lesions, adrenal, spleen, thymus, and liver tissues in the 1X group) on SD 37. The right and left ear canal with the middle and inner ears were necropsied and collected from all animals. Additionally, plasma samples were collected and analyzed for concentrations of florfenicol, terbinafine, and betamethasone.

h. Statistical Analysis: Analysis of variance was used to evaluate all continuous variables. Models included treatment, sex, and the treatment-by-sex interaction as fixed effects. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time, and treatment-by-sex-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate.

3. Results: All dogs were in good health with normal hearing throughout the study.

   a. Clinical findings included post administration ear wetness in all dogs in the 1X and 5X groups and unilateral, transient brown/red discharge from one ear in each of two dogs in the 5X group after the 4th application on SD 22. One dog in the 5X group also had erythema and auricular vascular dilatation at physical examination.

b. Plasma analysis for active substances: Low plasma concentrations of florfenicol, terbinafine, and betamethasone were measurable during the first 2-4 days in the 1X group and during the first 2- 7 days in the 5X group. On SD 8 and 15, there were no quantifiable plasma concentrations of any of the three active ingredients in the pre-dose samples of most of the dogs in the 1X group. Florfenicol and terbinafine (not betamethasone) were measurable in pre-dose samples on SD 8 and 15 in most of the dogs in the 5X group. The increases in mean plasma pharmacokinetic parameters were less than dose proportional for all three active ingredients on SD 1 and 8.

c. Body weight gain was lower (approximately 17%) in both the 1X and 5X groups compared to the control (0X) group.

d. Clinical pathology: One dog in the 5X group had lower lymphocyte counts. There was also elevated alanine aminotransferase (ALT) activity in three dogs in the 5X group, accompanied by minimal or mild microscopic hepatocellular vacuolation observed at necropsy in two of these dogs.

e. Adrenocorticotropic hormone (ACTH) stimulation: There was a decrease (within the normal reference range) in serum cortisol levels after ACTH stimulation in the 1X group which was not associated with clinical signs, organ weight, or microscopic changes. There was a decrease in serum cortisol levels after ACTH stimulation (below normal reference range) in the 5X group accompanied by decreased adrenal gland and thymic weights with minimal adrenal cortical atrophy and lymphoid depletion of the thymus. Changes in the 5X group were indicative of hypothalamic–pituitary-adrenal axis suppression typically seen with administration of exogenous corticosteroids.

f. Histopathology: Unilateral vesicle formation within the epithelium of the tympanic membrane was observed in two dogs in the 1X group, and in four dogs in the 5X group. In three dogs in the 5X group, there was unilateral mucosal necrosis and ulceration of the lining of the middle ear cavity. In two dogs this finding was associated with a unilateral, transient brown-red discharge noted after the 4th administration on SD 22. Decreased thymic weights in the 5X group were associated with slight (in three dogs) or moderate (in one dog also noted with slightly lower lymphocyte counts) lymphoid depletion of the thymus.

4. Conclusions: This study supports the safe use of OSURNIA when administered at 1 mL per ear dosed twice, seven days apart. Aural administration of OSURNIA (6 administrations in 5 weeks) to approximately 4 month old mixed breed hounds at 1X (1mL/ear or 2 mL/dog with repeated administration every 7 days) and 5X (5 mL/ear or 10 mL/dog with repeated administration every 7 days) the recommended dose was associated with ear wetness, decreased weight gain, and alterations of the hypothalamic-pituitary-adrenal axis as evidenced by the ACTH stimulation results. Other findings considered to be related to the aural administration of OSURNIA at 5X the recommended dose include elevated ALT, lymphopenia, decreased adrenal gland and thymic weights, and unilateral mucosal necrosis and ulceration of the lining of the middle ear cavity.

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 OSURNIA:

Human Warnings are provided on the product label as follows: **"**Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. In case of accidental skin contact, wash area thoroughly with water. Avoid contact to the eyes."

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

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

OSURNIA, 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 OSURNIA.

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

November 4, 2014- Original Version

November 4, 2016:

- Under B. Substantial Evidence, 2. Field Study Effectiveness, d. Results; the percent effectiveness rates of 63.7% for OSURNIA and 41.7% for placebo are incorrect based on the numbers provided in Table 2: Day 45 Effectiveness Summary. The percent effectiveness was updated to 64.78% for OSURNIA and 43.42% for placebo to be consistent with Table 2.