

Date of Approval: October 11, 2023

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-572

AYRADIA™

(metronidazole oral suspension)

Dogs

AYRADIA™ oral suspension is indicated for the treatment of *Giardia duodenalis* infection in dogs.

Sponsored by:

Virbac AH, Inc.

Executive Summary

AYRADIA™ (metronidazole oral suspension) is approved for the treatment of *Giardia duodenalis* infection in dogs. AYRADIA™ is an antimicrobial drug that is administered twice daily for 5 consecutive days using the supplied syringe.

Safety and Effectiveness

The sponsor conducted one laboratory study and one field study to demonstrate the effectiveness of AYRADIA™ to treat naturally occurring *Giardia* infections. In the laboratory study, young, healthy, male and female beagles were administered either AYRADIA™ or sterile water (negative control) orally twice daily for 5 consecutive days starting on Day 0. On Day 8 (4 days after the last treatment), trophozoites were counted in each dog's small intestine. Trophozoites are the active, motile, growing stage in the life cycle of certain protozoan parasites, including those in the *Giardia* group. Dogs in the treated group had significantly lower trophozoite counts compared to dogs in the control group. AYRADIA™ was over 99% effective at reducing *Giardia* trophozoites in treated dogs. There were no adverse events during the study.

In the field study, privately owned dogs and shelter dogs with naturally occurring *Giardia* infections were enrolled. The dogs were intact and neutered males and females of various breeds, ages, and weights. They received either AYRADIA™ or a vehicle control in a 2:1 ratio for 5 consecutive days starting on Day 0. The vehicle control contained all the inactive ingredients in AYRADIA™ but contained no metronidazole. Fecal samples were obtained from each dog on 3 consecutive days before (Days -3, -2, and -1) and after (Days 5, 6, and 7) treatment. *Giardia* cyst counts for each sample were determined by fecal immunofluorescent assay, or IFA. Cysts are the inactive, non-motile stage of the parasite's life cycle that are passed in the feces and can cause infections in other hosts. Dogs in the treated group had significantly lower post-treatment cyst counts compared to dogs in the control group. AYRADIA™ was over 99% effective at reducing *Giardia* cysts in treated dogs. The most common adverse events seen during the study were vomiting and diarrhea, which were generally isolated and resolved without treatment. Because of the relatively low incidence of gastrointestinal adverse events, it was not possible to directly associate the vomiting and diarrhea with the drug.

The sponsor conducted a margin of safety laboratory study in young, healthy, male and female beagles. The dogs were administered AYRADIA™ orally at 0X, 1X, 2X, or 3X the labeled dose for 15 consecutive days (3X the labeled duration); or 5X the labeled dose for 5 consecutive days (the labeled duration). Dogs in the 5X group had increased episodes of ear erythema and diarrhea compared to the other groups. Both the ear erythema and diarrhea resolved without treatment.

The sponsor conducted two laboratory tolerance studies in a total of six young, healthy dogs. Two dogs received an investigational metronidazole oral suspension (not the final formulation) at 5X the labeled dose for 7 days. One of the dogs vomited bile on Day 4, but otherwise, neither dog had any adverse events. Two dogs received a commercially-available metronidazole tablet, which is approved for use in people, at 5X the labeled dose for 7 days. Neither dog had any adverse events. Two dogs received an investigational metronidazole oral suspension (not the final formulation) at 10X the labeled dose for 7 days. By Days 7 and 8, both dogs showed severe neurologic signs, including ataxia and lack of ocular reflexes. One of the dogs also exhibited lateral

movements of the head and eyes, recumbency, tremors, and mydriasis. The metronidazole was stopped, and repeated doses of diazepam and furosemide were given. Both dogs fully recovered within approximately 24 hours.

The sponsor also conducted a field effectiveness and safety study in client-owned dogs with naturally occurring *Giardia* infections. The dogs were intact and neutered males and females of various breeds, ages, and weights. About half the dogs were treated with AYRADIA™ and about half with a positive control (another antiprotozoal drug) at the labeled dose and duration. The most common adverse events in dogs treated with AYRADIA™ were vomiting and diarrhea, which resolved without treatment. No adverse neurologic signs were seen during the study.

User Safety

AYRADIA™ is not a dermal or eye irritant but is a skin sensitizer. In case of skin contact, the affected area should be washed thoroughly. People who come in contact with a treated dog's saliva during the first five minutes after administration should wash their hands. If the drug has been applied to dog food, the dog food should be kept away from children until after the dog has finished eating.

Conclusions

Based on the data submitted by the sponsor for the approval of AYRADIA™, 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 141-572

B. Sponsor

Virbac AH, Inc.
PO Box 162059
Fort Worth, TX 76161

Drug Labeler Code: 051311

C. Proprietary Name

AYRADIA™

D. Drug Product Established Name

metronidazole oral suspension

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Suspension

G. Amount of Active Ingredient

125 mg/mL

H. How Supplied

30 mL and 100 mL bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

25 mg/kg (11.3 mg/lb) of body weight, using the supplied syringe, twice daily for five consecutive days

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

AYRADIA™ oral suspension is indicated for the treatment of *Giardia duodenalis* infection in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

A dose of 25 mg metronidazole oral suspension/kg body weight (BW) administered orally, twice a day for 5 days was chosen based on a dose determination study conducted with 40 naturally-infected, asymptomatic dogs between 8 and 12 weeks of age. At study initiation, the dogs were confirmed to be shedding *Giardia* cysts by fecal immunofluorescence assay (IFA). On Day -1, dogs were randomized based on cyst counts and allocated to one of four groups (n = 10 per group). Dogs assigned to Group 1 were administered a vehicle control¹ product. Dogs assigned to Groups 2, 3, and 4 were administered a non-final formulation of metronidazole oral suspension (160 mg/mL) at a dose rate of 12.5 mg/kg twice daily, 25 mg/kg twice daily, and 50 mg/kg twice daily, respectively. All dogs were dosed twice daily (approximately 12 hours apart) for five days (Day 0 through Day 4). Fecal samples were collected daily for 10 days (from Day 2 through Day 11) from each dog for analysis by IFA. The response to treatment was evaluated by comparison of the IFA cyst counts in dogs treated with the metronidazole oral suspension to the cyst counts in control dogs. Metronidazole oral suspension reduced cumulative cyst counts in the three metronidazole treatment groups compared to the control group on all fecal sampling days (Day 5 through Day 11). In the control group, cumulative cyst excretion had increased to above 180,000 cysts by Day 11, while cumulative cyst excretion remained below 5,000 up to Day 11 for Group 2 (12.5 mg/kg), and below 500 for Groups 3 (25 mg/kg) and 4 (50 mg/kg). Based on the results of 90% effectiveness from Day 2 through Day 11, a dose of 25 mg/kg twice daily of metronidazole oral suspension was selected for use in dogs naturally infected with *Giardia duodenalis*.

¹ The vehicle control contained all the inactive ingredients in AYRADIA™ but contained no metronidazole (the active ingredient).

Table II.1. Cumulative Geometric Mean Cyst Count in the Control and Metronidazole Oral Suspension Treatment Groups From the Day After the Last Treatment (Day 5) Through Day 11.

Group (Dosage)	Study Day 5	Study Day 6	Study Day 7	Study Day 8	Study Day 9	Study Day 10	Study Day 11
Group 1 (vehicle control)	6323	16202	42324	72750	83214	116592	186519
Group 2 (12.5 mg/kg)	20	92	184	460	913	2790	4341
Group 3 (25 mg/kg)	3	11	26	55	55	154	448
Group 4 (50 mg/kg)	18	32	125	162	171	177	301

The means were calculated using the cysts per gram (CPG) for each animal by adding up the cyst count from Study Days 5 - 11. These values were used to calculate the geometric mean cumulative cyst excretion per group.

B. Substantial Evidence

The effectiveness of AYRADIA™ was demonstrated in one dose confirmation laboratory study and one field effectiveness and safety study. AYRADIA™ was administered at a dose of 25 mg/kg twice daily for 5 consecutive days in both studies. The *Giardia duodenalis* found in dogs in Europe are indistinguishable from the parasite found in the United States. Therefore, a multi-site field study performed in Europe was acceptable to support substantial evidence of effectiveness for the United States.

1. Laboratory Dose Confirmation Study.

Title: Dose Confirmation of Study 409.01, Evaluating Trophozoites in Dogs with Naturally Occurring *Giardia duodenalis* Infection.
 (Study No. U-409.010000-60005)

Study Dates: July 2, 2018 to March 6, 2019

Study Location: Waverly, New York

Study Design:

Objective: To confirm the effectiveness of AYRADIA™ (metronidazole oral suspension) administered at 25 mg/kg every 12 hours for five consecutive days, as a treatment for naturally occurring infection with *Giardia duodenalis* in dogs.

Study Animals: 13 healthy beagle dogs (12 males and 1 female) naturally infected with *Giardia* based on pre-treatment cyst counts of ≥ 750 cysts/gram of feces. The dogs were between 8.1 and 10.9 months of age and weighed between 9.8 and 14.6 kg.

Experimental Design: The study was a parallel, masked study design. Dogs were assigned to 7 blocks (2 dogs per block) according to the ranking of their pre-study cyst count and assigned to treatment groups within blocks in a 1:1 ratio. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines [FDA Guidance for Industry (GFI) 85, Veterinary International Conference on Harmonization (VICH) GL9 Good Clinical Practices].

Drug Administration: Beginning on Day 0, dogs were administered AYRADIA™ or sterile water (negative control) orally every 12 hours for 5 days as shown below in Table II.2.

Table II.2. Treatment Groups

Treatment Group	Dosage	Number and Sex of Animals
Sterile water (negative control)	0.2 mL/kg every 12 hours for five days	6 males*
AYRADIA™ (125 mg/mL)	25 mg/kg (0.2 mL/kg) every 12 hours for five days	7 (6 males and 1 female)

*One dog enrolled in the negative control group was removed from the study before dosing because it did not maintain an adequate cyst count (greater than or equal to 750 cysts/gram of feces) during study acclimation.

Measurements and Observations: The primary variable for effectiveness was the trophozoite count. General health observations were conducted once daily. At necropsy on Day 8, 4 days after the last dose, the small intestines were removed from each dog, processed, and trophozoites were counted.

Statistical Methods: For the analysis of effectiveness, a two-sided test was used at a significance level of 0.05. Trophozoite count for each dog was transformed to the natural logarithm of (count+1) for analysis. A mixed effect model including treatment group as a fixed effect and block as a random effect was used to compare trophozoite counts between the treated and the control groups.

Using the back-transformed least squares mean (LS mean) counts from the model, percent effectiveness was calculated as $100 * [(C-T)/C]$, where C is the geometric mean for the control group and T is the geometric mean for the treated group.

Result: AYRADIA™ was 99.7% effective against natural *Giardia* infections in dogs (Table II.3). A statistically significant difference in trophozoite counts was detected in the treated group as compared to the control group ($p = 0.0026$).

Table II.3. Trophozoite Count Results

Treatment Group	Range of Trophozoite Counts	Geometric Mean	Percent Effectiveness
Negative control	25,738 to 1,859,667	399,617	NA
AYRADIA™	71 to 31,548	1,056	99.7

Adverse Reaction: No treatment-related adverse events were recorded during the study.

Conclusion: The study demonstrated AYRADIA™ was effective against natural *Giardia duodenalis* infections in dogs.

2. Clinical Field Study

Title: Efficacy and Safety Study to Evaluate an Oral Suspension of Metronidazole (409.01) for the Treatment of *Giardia duodenalis* in Naturally Infected Dogs. (Study No. U-409.010000-60006)

Study Dates: April 1, 2020 to December 12, 2022

Study Locations:

Table II.4. Study Locations and Status of the Animals Enrolled

Location	Privately Owned or Shelter Animals
München, Germany	Privately Owned
Berlin, Germany	Privately Owned
Traunreut, Germany	Privately Owned
Ecser, Hungary	Shelter Housed
Paks, Hungary	Shelter Housed
Sobral de Monte Agraço, Portugal	Shelter Housed
Palmeira, Portugal	Shelter Housed
Amares, Portugal	Privately Owned
Braga, Portugal	Privately Owned
Pardilhó, Portugal	Privately Owned

Study Design:

Objective: The study objective was to evaluate the effectiveness and safety of AYRADIA™ (metronidazole oral suspension) at a dosage of 25.0 mg/kg BW administered orally twice daily for 5 consecutive days for the treatment of naturally occurring infections with *Giardia duodenalis* in dogs under field conditions.

Study Animals: One hundred eighty-nine (189) dogs were screened for the study at 10 study sites throughout Germany, Portugal, and Hungary. The dogs were of various pure and mixed breeds, were between 1.2 months and 15.2 years of age, and were between 2 and 37.2 kg body weight. The population consisted of both intact and neutered male and female dogs.

Experimental Design: The study was a randomized, masked, vehicle control study. The study followed a centralized randomization stratified by site type. An independent statistician prepared two randomization lists, one randomization list for shelters and one randomization list for veterinary clinics and balanced the randomization at the predefined AYRADIA™:control ratio of 2:1 using convenience blocks of size 3. The study was conducted in accordance with GCP guidelines.

Drug Administration: Beginning on Day 0, dogs were administered AYRADIA™ or vehicle control twice daily for 5 days, as shown below in Table II.5.

Table II.5. Treatment Groups, Dosage Regimens, and Number of Animals per Group

Treatment Group	Dosage Regimen	Number of Animals
AYRADIA™	25 mg/kg BW (0.2 mL/kg BW), using the supplied syringe, twice daily for a period of five consecutive days (Day 0 to Day 4)	121
Vehicle control	0.2 mL/kg BW, using the supplied syringe, twice daily for a period of five consecutive days (Day 0 to Day 4)	61

Measurements and Observations:

Physical examination and body weight were conducted on Day -3. Hematology, serum chemistry, and urinalysis parameters were assessed on Days -3 and 5. IDEXX *Giardia* SNAP Test and IDEXX Parvovirus SNAP Test were performed prior to enrollment (Day -3, -2, -1, or 0). A qualitative fecal flotation test to evaluate for intestinal parasites was performed prior to enrollment (Day -3, -2, -1, or 0). Fecal samples were obtained on 3 consecutive days before and 3 consecutive days after study treatment (Days -3 to -1 and Days 5 to 7) for the pretreatment (baseline) and post-treatment cyst counts, respectively. *Giardia* cyst counts for each sample were determined by IFA.

Statistical Methods:

Effectiveness was demonstrated if the study was successful for the following two analyses:

- 1) The Least Squares Means (LSMeans) of the AYRADIA™-treated group was significantly different and numerically smaller than the control group at a two-

side 5% level. For the comparison, a mixed model was used. The log-transformed mean of the three post-treatment cyst counts was included in the model as the dependent variable, the treatment group was included as the fixed effect, the mean of the three baseline cyst counts was included as a covariate, the type of site (veterinary clinics or shelter facilities) and treatment by type of site interaction were included as fixed effects, and the owner or owner proxy (for animals from shelter facilities) was included as a random effect.

- 2) AYRADIA™-treated group showed a ≥ 90% reduction in post-treatment cyst counts compared to baseline cyst counts using the following formula:

$$\text{percent reduction} = 100 * \frac{\text{pretreatment geometric mean} - \text{posttreatment geometric mean}}{\text{pretreatment geometric mean}}$$

The baseline geometric mean and post-treatment geometric mean cyst counts were calculated from two separate repeated measures mixed models (RMMM) applied on the AYRADIA™-treated dogs only. The models used logarithm-transformation [log(x+1)] of each cyst count as the dependent variable, type of site as the fixed effect, the owner/owner proxy as a random effect, and animal ID as the subject term. The geometric means were calculated from the back-transformed LSMeans of the cyst counts from the models minus one. Five covariance matrices of the residuals were considered (First Order Autoregressive, Unstructured, Toeplitz, Compound Symmetry and Variance Components). Selection of the matrix for the final analysis was based on the smallest Akaike information criterion (AIC).

Safety data were descriptively summarized, and adverse events were tabulated by treatment groups in frequency tables.

Results:

For the first analysis, the post-treatment cyst count in the AYRADIA™ group was significantly less than in the vehicle control group (p < 0.001). The log difference between the groups was -4.87.

For the second analysis, the percent reduction in cyst counts for the AYRADIA™ group was 99.9% (see Table II.6).

Table II.6. Giardia Cyst Counts and Percent Reduction Per Treatment Group

Treatment Group	Geometric Mean Cyst Counts Pre-treatment	Geometric Mean Cyst Counts Post-treatment	Percent Reduction [†]
AYRADIA™	1602.9	1.45387	99.91%
Vehicle control	2668.61	329.932	87.64%

[†]100 x (Pre Geometric Mean - Post Geometric Mean)/Pre Geometric Mean

The study met both primary endpoints for demonstrating effectiveness.

Adverse Reactions:

The most common drug-related adverse reactions reported during the study were diarrhea (8 dogs [6.7%] in the AYRADIA™ group, 3 dogs [5%] in the control group) and vomiting (5 dogs [4.2%] in the AYRADIA™ group, 2 dogs [3.3%] in the control group). Diarrhea and vomiting were generally isolated and self-limiting events during the study.

Hyperactivity was reported in one dog in the AYRADIA™ group.

Conclusion: AYRADIA™ was safe and effective when administered at 25 mg/kg BW for five consecutive days for the treatment of *Giardia duodenalis* in naturally infected dogs.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: Target Animal Safety Study in Puppies. (Study No. F-409.010000-40007)

Study Dates: November 16, 2015 to November 30, 2016

Study Location: Evreux, France

Study Design:

Objective: The objective of this study was to evaluate the safety of AYRADIA™ when administered orally to beagle puppies at one (1X), two (2X), or three (3X) times the intended dose for 15 consecutive days (three times the intended duration of treatment); or five (5X) times the intended dose for 5 consecutive days (the intended duration of treatment).

Study Animals: The study enrolled 40 healthy beagle dogs (20 males and 20 females) approximately 12 weeks of age at the start of treatment and weighing between 3 to 4.7 kg.

Experimental Design: The study used a masked, negative controlled, parallel design. The dogs were assigned, based on their body weight, to one of the five treatment groups shown in Table III.1. The animals were ranked by body weight in ascending order and allocated to the treatment groups by putting the lowest to highest body weights in groups 1 to 5 in the following pattern: group 1, 2, 3, 4, 5; then group 5, 4, 3, 2, 1; then group 1, 2, 3, 4, 5; etc. The dogs were then randomized to their cages. Male dogs were acclimated for 9 days before the start of treatment and female dogs were acclimated for 10 days before the start of treatment. Day 0 represented the start of drug administration for each dog. This study was conducted in accordance with Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) Regulations.

Table III.1. Treatment (Tx) Groups and Drug Administration

Tx Group	Dose mg/kg (Dose Multiple)	Treatment Duration	Number and Gender of Animals
Group 1	0 mg/kg (0X; negative control)	15 days	4 males and 4 females
Group 2	25 mg/kg (1X)	15 days	4 males and 4 females
Group 3	50 mg/kg (2X)	15 days	4 males and 4 females
Group 4	75 mg/kg (3X)	15 days	4 males and 4 females
Group 5	0 mg/kg, then 125 mg/kg (0X, then 5X)	10 days at 0 mg/kg, then 5 days at 125 mg/kg	4 males and 4 females

Drug Administration: Dogs were administered AYRADIA™ (metronidazole oral suspension) or control (unmedicated drinking water) orally every 12 hours for 15 days as listed in Table III.1. The dogs were fasted for at least 6 hours before each dose administration to ensure maximal drug absorption. The administered dose was based on the most recently recorded body weight.

Measurements and Observations: Each dog was observed for general health observations at least twice daily throughout the study, including the acclimation period. In addition, during the treatment period, each animal was observed eight times a day for the recording of clinical signs: within 2 hours before each administration and 2, 4, and 6 hours after each administration. A veterinarian performed a complete physical examination on each dog once during the acclimation period, 2 hours after the first daily treatment on Days 1, 6, and 11, and before study conclusion on Day 16. The body weight of each animal was recorded on Days -9 (males), -10 (females), -7, -1, 6, 11, and 16. Food consumption was recorded daily (at the time of food removal) from Day -6 until Day 15. The amount of water consumed by each dog was recorded daily, from Day -6 until Day 15. Blood samples and urine collection for clinical pathology (hematology, blood biochemistry, C-Reactive Protein [CRP], and urine) were collected once before the beginning of the treatment period and on the last day of the study, Day 16. At the end of the study, dogs were euthanized and necropsied for gross pathology and histopathology evaluation.

Statistical Method: Because the animals were not randomly assigned to the treatment groups, inferential statistical analyses were not performed. Endpoints were summarized for each treatment group pooled over sex and by sex.

Results: There was an increased number of dogs with ear erythema and diarrhea, and an increased number of observations of ear erythema and diarrhea, in the highest dose group (Group 5) compared to the control and lower dose groups (see

Tables III.2, III.3, and III.4 below). These effects were self-limiting and did not require veterinary intervention.

Table III.2. Number of Dogs with Abnormal Skin and Feces-Related Health Observations

Observation	Group 1 (n = 8)	Group 2 (n = 8)	Group 3 (n = 8)	Group 4 (n = 8)	Group 5 (n = 8)
Skin (ear) erythema, well-defined	0	0	1	1	2
Soft or liquid stools, moderate or marked	4	2	2	3	7

Table III.3. Number of Observations of Erythema of the Ears by Group and Severity During Days 1 to 16

Observation	Group 1	Group 2	Group 3	Group 4	Group 5
Very slight erythema	11	4	4	15	30
Well-defined erythema	0	0	2	5	12
Total	11	4	6	20	42

Table III.4. Number of Abnormal Feces Observations by Group and Severity During Days 1 to 16

Observation	Severity	Group 1	Group 2	Group 3	Group 4	Group 5
Soft feces	Marked	7	0	0	2	31 (8 ^a)
Soft feces	Moderate	23	9	13	10	100 (49 ^a)
Soft feces	Slight	62	8	26	54	67 (44 ^a)
Liquid feces	Moderate	0	3	0	0	11 (9 ^a)
Liquid feces	Slight	0	4	0	1	13 (0 ^a)
Total	All	92	24	39	67	221 (110^a)

^aAbnormal observations on Days 11 to 16, the days of metronidazole administration for Group 5

Conclusions: This study supports the safe use of AYRADIA™ (metronidazole oral suspension) at 25 mg/kg twice daily in dogs for 5 consecutive days for the treatment of *Giardia duodenalis* infection. Treatment with AYRADIA™ at five times the intended dosage was associated with self-limiting episodes of diarrhea and of erythema of the ears.

B. Tolerance Study

In a two-dog laboratory tolerance study (Study F-409.010000-60002), 2 female dogs, approximately 8 months of age, received 250 mg/kg/day (5X the intended daily dose) for 7 days of an investigational formulation of metronidazole oral suspension (160 mg/mL). Clinical observations, physical examination observations, and food consumption were recorded for this study. Metronidazole was administered to the dogs in the fed state. Clinical pathology and gross pathology were not evaluated in this study. One of the 2 dogs vomited bile the morning of Day 4. The dogs exhibited no other adverse clinical effects.

C. Tolerance Study

To further evaluate the safety of an investigational formulation of metronidazole oral suspension (160 mg/mL), a four-dog laboratory tolerance study was conducted (Study F-409.010000-60003). Two dogs, approximately 4 months old, received an investigational metronidazole oral suspension formulation (160 mg/mL) at 500 mg/kg/day (10X the intended daily dose) for 7 days, and 2 dogs (one 12 months old and one 21 months old) received a commercially-available metronidazole tablet, which is approved for people, at 250 mg/kg/day (5X the intended daily dose) for 7 days. Metronidazole was administered to the dogs in the fed state. No abnormal clinical signs were observed in animals treated at 250 mg/kg/day with the metronidazole tablet. The 2 dogs that received the metronidazole oral suspension at 500 mg/kg/day exhibited severe neurologic signs by Days 7 and 8. Ataxia and lack of ocular reflexes were observed in both dogs. Additional adverse signs in one of the dogs included lateral movements of head and eyes, recumbency, tremors, and mydriasis. The dogs recovered after cessation of metronidazole administration and treatment with repeated doses of diazepam and furosemide. Both dogs recovered fully within approximately 24 hours.

D. Field Effectiveness and Safety Study

The safety of AYRADIA™ (metronidazole oral suspension) was evaluated in a masked, active-controlled, 8-day, multi-site field study (Study F-409.010000 60009) to evaluate the effectiveness of metronidazole for the treatment of *Giardia duodenalis* infection in dogs. The field study enrolled 186 client-owned dogs diagnosed with giardiasis from 44 veterinary clinics evenly distributed between France and Germany. The enrolled population consisted of 104 male (84 intact, 20 neutered) and 82 female (66 intact, 16 neutered) dogs between 1.8 months and 13.4 years of age and of various pure (about 75%) or mixed (about 25%) breeds. Of the 186 enrolled dogs, 91 dogs were treated with the AYRADIA™ at 25 mg/kg twice daily for 5 days, 89 dogs were treated with an active control veterinary product, and 6 dogs were removed prior to treatment.

The most commonly reported adverse reactions in dogs treated with AYRADIA™ were vomiting and diarrhea. Of the 91 dogs treated with AYRADIA™, 13 (14.3%) exhibited vomiting, and 3 (3.3%) exhibited diarrhea.

Other less frequently observed gastrointestinal related signs included hypersalivation, abdominal pain, anorexia, and lethargy. Each of these occurred with vomiting, and thus, were considered signs of the general gastrointestinal irritation.

One dog treated with AYRADIA™ experienced polyuria and polydipsia, which may have been a temporary increase in drinking associated with drug administration. Another dog in the AYRADIA™ group experienced head shaking and reddening of the auditory passages and was diagnosed with otitis externa. No adverse neurologic signs were reported during this study.

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 AYRADIA™:

Keep out of reach of children. Not for use in humans. Metronidazole has been found to cause cancer in laboratory animals; however, there is inadequate evidence of carcinogenicity in humans. People with known sensitivity to metronidazole or other nitroimidazole derivatives should avoid contact with AYRADIA™ oral suspension. This product is not a dermal or eye irritant but is a skin sensitizer, which can potentially cause allergic contact dermatitis. Wash hands after use. Avoid contact with skin. In case of skin contact, wash the affected area thoroughly. Persons who come in contact with the dog's saliva during the first five minutes after administration should wash their hands. If the drug has been applied to dog food, the dog food should be kept away from children until after the dog has finished eating. Avoid accidental ingestion. In case of accidental ingestion, seek medical advice immediately.

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 AYRADIA™, 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 *Giardia duodenalis* infection in dogs and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

AYRADIA™, as approved in our approval letter, qualifies for FIVE 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 this is the first time we are approving this active moiety in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information

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

VII. APPENDIX

On **DATE**, the formula in Section II.B.2.2), which describes how the percent reduction in the AYRADIA™-treated group was calculated, was revised. The formula now reads:

$$\text{percent reduction} = 100 * \frac{\text{pretreatment geometric mean} - \text{posttreatment geometric mean}}{\text{pretreatment geometric mean}}$$

The original formula read:

$$\text{percent reduction} = 100 * \frac{\text{baseline geometric mean} - \text{posttreatment geometric mean}}{\text{posttreatment geometric mean}}$$