Date of Approval: February 3, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-600

WORMX

pyrantel pamoate

Flavored Tablets

Dogs

For removal of: Hookworms in Puppies and Dogs (*Ancylostoma caninum*; *Uncinaria stenocephala*) Large Roundworms (Ascarids) in Puppies and Dogs (*Toxocara canis*; *Toxascaris leonina*) To Prevent Reinfection of Large Roundworms in Puppies, Adult Dogs and Lactating Bitches after Whelping (*Toxocara canis*).

Sponsored by:

ECO LLC

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-600

B. Sponsor

ECO LLC
344 Nassau St.
Princeton, NJ 08540

Drug Labeler Code: 066916

C. Proprietary Name

WORMX

D. Product Established Name

Pyrantel pamoate

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Flavored tablet

G. Amount of Active Ingredient

Each tablet contains pyrantel pamoate equivalent to 22.7 mg or 113.5 mg pyrantel base

H. How Supplied

2 x 22.7 mg and 12 x 22.7 mg packages for puppies and small dogs
2 x 113.5 mg and 12 x 113.5 mg packages for large dogs

I. Dispensing Status

OTC

J. Dosage Regimen

22.7 mg tablet in puppies and small dogs
For the removal of large roundworms (Ascarids) and hookworms, give 1 tablet for each 10 lb of body weight. Dosage is designed to provide at least 2.27 mg per pound body weight for dogs weighing over 5 lb, and at least 4.54 mg per pound of body weight for dogs weighing 5 lb or less. For dogs weighing more than 10 lb, tablets may be broken in half to provide ½ tablet for each additional 5 lb of body weight.

113.5 mg tablet in large dogs
For the removal of large roundworms (Ascarids) and hookworms in adult dogs or young dogs weighing more than 25 lb, administer tablets according to the weight of the animal:

Weight of Animal	Number of Tablets
25 lb	½ Tablet
26 lb to 50 lb	1 Tablet
51 lb to 75 lb	1 ½ Tablets
76 lb to 100 lb	2 Tablets

For dogs weighing less than 25 lb, use WORMX 22.7 mg tablets for puppies and small dogs.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

For removal of: Hookworms in Puppies and Dogs (*Ancylostoma caninum*; *Uncinaria stenocephala*) Large Roundworms (Ascarids) in Puppies and Dogs (*Toxocara canis*; *Toxascaris leonina*) To Prevent Reinfection of Large Roundworms in Puppies, Adult Dogs and Lactating Bitches after Whelping. (*Toxocara canis*)

N. Reference Listed New Animal Drug

D-WORM; pyrantel pamoate; NADA 139-191; Farnam Companies, Inc.

II. BIOEQUIVALENCE:

For this ANADA, two clinical endpoint studies were conducted to demonstrate product bioequivalence using the generic and RLNAD pyrantel pamoate flavored tablets. One study was conducted using the 22.7 mg tablet strength, and one was conducted using the 113.5 tablet strength. The study information is summarized below.

A. 22.7 mg Clinical Endpoint Bioequivalence Study

A single site, masked, controlled clinical endpoint bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of pyrantel pamoate 22.7 mg flavored tablets in dogs.

1. Title:
   "Clinical End Point Study to Determine the Bioequivalence of ECO Animal Health's Pyrantel Pamoate Tablet Compared to Farnam's D-Worm Dog Wormer Chewable Tablets: Anthelmintic Efficacy Against Induced Toxocara canis Infections in Dogs"

2. Testing Facilities: East Tennessee Clinical Research, Inc., Knoxville, TN.

3. Objective:
   The objective of the study was to determine the bioequivalence of ECO Animal Health's 22.7 mg generic pyrantel pamoate flavored tablets and Farnam Companies, Inc.'s 22.7 mg D-WORM (pyrantel pamoate) Chewable Tablets.

4. Animals:
   24 juvenile intact male beagle dogs

5. Experimental Design:
   The experimental design was a masked, controlled clinical end point bioequivalence study

6. Treatment:
   The test animals were orally infected with larvated *Toxocara canis* eggs. Twenty-four infected animals, ranked by fecal egg counts, were randomly allocated to test, reference, and control groups (8 dogs per group). Dogs received their respective test (generic product), reference (RLNAD), and control (no drug) treatments.

7. Measurement and Observation:
   Fecal egg counts were completed on the appropriate days after treatment. Total postmortem worm counts were collected at the completion of the study. Animal observations were made throughout the study for assessment of general health and adverse events. All animals remained healthy during the study. Reported adverse events included worms in feces and/or soft feces, and one report of vomiting. These observations occurred in test, reference, and control groups and are considered a normal physiological response to parasitism and deworming.

8. Statistical Methods:
   The primary variable was the recovered worm count from necropsy on Study Day 10. A two-sided Wilcoxon rank sum test (the NPAR1WAY procedure in SAS, Version 9.2) was used to compare the number of worms at necropsy for each of the generic and RLNAD groups to the untreated control group. Each test was conducted using a 0.05 level of significance.

   Percent effectiveness for each treated group was calculated as follows:

   $$[(\text{GM control group} - \text{GM treated group})/\text{GM control group}] \times 100\%$$

   where GM is the geometric mean based on the transformation ln(count +1), and where "ln" is the natural logarithm.

   The secondary variable was Day 10 fecal egg counts. For each of the generic and RLNAD groups, egg counts were compared with the untreated group using a two-sided Wilcoxon rank sum test. Each test was conducted using a 0.05 level of significance.

   The two products were considered bioequivalent based on the following:
   a. An adequate infection was established. Regulatory guidelines for this model system define "adequacy of infection" as at least 6 control animals exhibited 5 or more specimens of *T. canis* per dog (VICH GL 19/CVM Guidance for Industry 111).

b. Using a two-sided Wilcoxon rank sum test with a 0.05 level of significance, both the RLNAD and generic mean scores for recovered worm counts were statistically significantly different from that of the control ($p<0.05$).
c. The percent effectiveness for both generic and RLNAD treatments exceeded 90%.

Based on Wilcoxon's rank sum test, worm counts in animals from the control group were significantly different from those of both treated groups. The p-values for comparison between control to the generic drug group and RLNAD group were 0.0057 and 0.0052, respectively. The percent effectiveness of ECO Animal Health's generic pyrantel pamoate chewable tablet was 90.7% and Farnam's D-Worm pyrantel pamoate chewable tablet was 91.1%. The study results for worm counts on Day 10 are presented in Table 1 below.

Table 1. Wilcoxon's Rank Sum Test – Worm counts on Day 10

Comparison	P-value	GM-Control	GM-treated	% Efficacy
Control vs. ECO	0.0057	13.1026	1.2247	90.6531
Control vs. Farnam	0.0052	13.1026	1.1635	91.1201

GM = geometric mean

Based on Wilcoxon's rank sum test, fecal egg counts in animal from the control group were significantly different from those of the treated groups. The p-values for comparison between control to the generic drug group and RLNAD group were 0.0139 and 0.0112, respectively. The study results for egg counts on Day 10 are presented in Table 2 below.

Table 2. Wilcoxon's Rank Sum Test – Fecal Egg Counts on Day 10

Comparison	P-value	GM-Control	GM-treated
Control vs. ECO	0.0139	341.564	29.638
Control vs. Farnam	0.0112	341.564	28.599

GM = geometric mean

9. Conclusion:
The generic 22.7 mg pyrantel pamoate flavored tablet is bioequivalent to the RLNAD (22.7 mg Farnam D-WORM Chewable Tablets) based on mean recovered worm counts and percent effectiveness, when administered orally to dogs at a dose of 5 mg/kg body weight.

B. 113.5 mg Clinical Endpoint Bioequivalence Study

One clinical endpoint bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of pyrantel pamoate 113.5 mg flavored tablets in dogs.

1. Title:
"Clinical End-Point Study to Determine the Bioequivalence of ECO Animal Health's 113.5 mg Pyrantel Pamoate Tablet Compared to Farnam's 113.5 mg D-Worm™ Dog Wormer Chewable Tablets: Anthelmintic Efficacy Against Induced *Toxocara canis* Infections in Large Dogs (26 or more lbs.)"

2. Testing Facility: East Tennessee Clinical Research, Inc., Knoxville, TN.

3. Objective:
   The objective of the study was to determine the bioequivalence of ECO Animal Health's 113.5 mg generic pyrantel pamoate flavored tablets and Farnam Companies, Inc.'s 113.5 mg D-WORM (pyrantel pamoate) Chewable Tablets.

4. Animals:
   30 juvenile intact male mongrel dogs

5. Experimental Design:
   The experimental design was a masked, controlled clinical end point bioequivalence study

6. Treatment:
   The test animals were experimentally infected orally with larvated *Toxocara canis* eggs. Thirty infected animals, ranked by fecal egg counts, were randomly allocated to test, reference, and control groups (10 dogs per group). Dogs received their respective test, reference, and control treatments.

7. Measurement and Observation:
   Fecal egg counts were completed on the appropriate days. Total postmortem worm counts were collected at the completion of the study. Animal observations were made throughout the study for assessment of general health and adverse events. All animals remained healthy during the study. Reported adverse events included worms in feces, bloody and/or bloody mucous in feces, and vomiting. These observations occurred in test, reference, and control treatment groups and are considered a normal physiological response to parasitism and deworming.

8. Statistical Methods:
   The primary variable was the recovered worm count from necropsy on Study Day 10. A two-sided Wilcoxon rank sum test (the NPAR1WAY procedure in SAS, Version 9.2) was used to compare the number of worms at necropsy for each of the generic and RLNAD groups to the untreated control group. Each test was conducted using a 0.05 level of significance.

   Percent effectiveness for each treated group was calculated as follows:

   $$[(\text{GM control group} - \text{GM treated group})/\text{GM control group}] \times 100\%$$

   where GM is the geometric mean based on the transformation ln(count +1), and where "ln" is the natural logarithm.

   The secondary variable was Day 10 fecal egg counts. For each of the generic and RLNAD groups, egg counts were compared with the untreated group using a two-sided Wilcoxon rank sum test. Each test was conducted using a 0.05 level of significance.

   The two products were considered bioequivalent based on the following:
   a. An adequate infection was established. Regulatory guidelines for this model system define "adequacy of infection" as at least 6 control animals exhibited 5 or more specimens of *T. canis* per dog (VICH GL 19/CVM Guidance for Industry 111).

b. Using a two-sided Wilcoxon rank sum test with a 0.05 level of significance, both the RLNAD and generic mean scores for recovered worm counts were statistically significantly different from that of the control ($p<0.05$).
c. The percent effectiveness for both generic and RLNAD treatments exceeded 90%.

Based on Wilcoxon's rank sum test, worm counts in animals from the control group were significantly different from those of both treated groups. The p-values for comparison between control to the generic drug group and RLNAD group were 0.0009 and 0.0024, respectively. The percent effectiveness of ECO Animal Health's generic pyrantel pamoate chewable tablet was 99.6% and Farnam's D-Worm pyrantel pamoate chewable tablet was 93.3%. The study results for worm counts on Day 10 are presented in Table 3 below.

Table 3. Wilcoxon's Rank Sum Test – Worm counts on Day 10

Comparison	P-value	GM-Control	GM-treated	% Efficacy
Control vs. ECO	0.0009	19.2805	0.0718	99.6277
Control vs. Farnam	0.0024	19.2805	1.2826	93.3476

GM = geometric mean

Based on Wilcoxon's rank sum test, fecal egg counts in animals from the control group were significantly different from those of the treated groups. The p-values for comparison between control to the generic drug group and RLNAD group were 0.0036 and 0.0314, respectively. The study results for egg counts on Day 10 are presented in Table 4 below.

Table 4. Wilcoxon's Rank Sum Test – Fecal Egg Counts on Day 10

Comparison	P-value	GM-Control	GM-treated
Control vs. ECO	0.0036	42.4966	0.5060
Control vs. Farnam	0.0314	42.4966	4.2687

GM = geometric mean

9. Conclusion:
The generic 113.5 mg pyrantel pamoate flavored tablet is bioequivalent to the RLNAD (113.5 mg Farnam D-WORM Chewable Tablets) for mean recovered worm counts and percent effectiveness, when administered orally to dogs at a dose of 5 mg/kg body weight.

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY:

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in dogs, which are not food producing animals.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to WORMX:

Keep out of reach of children.
Not for human consumption.

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that WORMX, when used according to the label, is safe and effective.