Date of Approval: Jan. 03, 2001

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

ANADA 200-281

Wormexx™
(pyrantel pamoate) Flavored Tablets For Puppies and Dogs

For the removal of large roundworms (ascarids) (*Toxocara canis*; *Toxascaris leonina*) and Hookworms (*Ancylostoma caninum*; *Uncinaria stenocephala*) in dogs and puppies. To prevent reinfection *of Toxocara canis* in puppies and adult dogs and in lactating bitches after whelping.

Sponsored by:

Blue Ridge Pharmaceuticals, Inc.,
A Subsidiary of Idexx Laboratories, Inc.
4249 Piedmont Parkway
Greensboro, North Carolina 27410

1. GENERAL INFORMATION:

ANADA: 200-281

Sponsor: Blue Ridge Pharmaceuticals, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

Generic Name: Flavored Pyrantel Pamoate Tablets

Trade Name: To be determined

Dosage Form: Flavored, Chewable Tablets

How Supplied: Two tablet sizes - a 22.7 mg tablet for dogs up to 25 lbs. and a 113.5 mg tablet for dogs weighing 25 lbs or greater. The tablets will be packaged in plastic (HDPE) bottles containing 100 of the 22.7 mg tablets and 50 of the 113.5 mg tablets.

How Dispensed: OTC

Amount of Active Ingredients: Small tablet contains 22.7 mg of pyrantel base as pyrantel pamoate; large tablet contains 113.5 mg of pyrantel base as pyrantel pamoate

Route of Administration: Oral

Species: Canine

Labeled Dosage: A minimum of 2.27 mg pyrantel base/lb. of body weight (5mg/kg) for dogs weighing over 5 lbs. and a minimum of 4.54 mg pyrantel base/lb. of body weight (10mg/kg) for dogs weighing 5 lbs. or less.

Small tablets (22.7 mg): give one tablet for each 10 lbs. of body weight. For dogs weighing more than 10 lbs., tablets may be broken in half to provide ½ tablet for each additional 5 lbs. body weight.

Large tablets (113.5 mg): for dogs weighing more than 25 lbs., see dosing chart below:

Weight (lbs.)	Number of Tablets
25	½
26 to 50	1
51 to 75	1 ½
76 to 100	2

Indications for Use: For the removal of large roundworms (ascarids) (*Toxocara canis; Toxascaris leonina*) and hookworms (*Ancylostoma caninum; Uncinaria stenocephala*) in dogs and puppies. To prevent reinfection of *Toxocara canis* in puppies and adult dogs and in lactating bitches after whelping.

Pioneer Product: D-Worm™ Dog Wormer Chewable Tablets, NADA 139-191, Farnam Company.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Restoration Act (53 FR 50460, December 15, 1988, First GADPTRA Policy Letter) an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). Under the Act, approval of a generic product requires a demonstration of bioequivalence to the pioneer product. Bioequivalence of the generic and pioneer products can be demonstrated by a clinical end-point study (61 FR 26182, May 24, 1996; Bioequivalence Guidance). The ANADA relies on the target animal safety and drug effectiveness data in the pioneer's New Animal Drug Application (NADA).

***Effectiveness*:**

The effectiveness of flavored pyrantel pamoate has been established by data contained in the approved NADA 139-191 (D-Worm™, Farnam), which referenced NADA 101-331. The following clinical end-point study established the therapeutic bioequivalence of the generic, Blue Ridge Pharmaceutical's Wormexx™, to the pioneer, Farnam's D-Worm™. A clinical endpoint study is preferred for the testing of the bioequivalence of pyrantel pamoate formulations in dogs, because the drug is not well-absorbed systemically and the desired effect is not dependent on systemic absorption, but rather a local effect in the intestinal tract.

A. Study Title: Clinical End-Point Bioequivalence Study Using Flavored Pyrantel Pamoate Tablets in Dogs with Artificially Induced Roundworm *(Toxocara canis)* Infections

Sponsor: Blue Ridge Pharmaceuticals, Inc.,
A subsidiary of Idexx Laboratories, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

Testing Facility: CHK – R&D
17190 Polk Road
Stanwood, MI 49346

Investigator: Dr. Dwight Bowman

Objective: To compare the efficacy of Wormexx™ to the pioneer product, Farnam's D-Worm™ and to establish bioequivalence on the basis of relative percent efficacy values against *T. canis,* considered to be the parasite in dogs which is most resistant to the effects of pyrantel pamoate and listed on the approved label.

Study Summary: Forty-two Beagle dogs (21 males and 21 females) were obtained from a USDA licensed supplier. At inoculation, the dogs were 9 to 10 weeks of age and weighed between 8.95 and 17.0 pounds. All the dogs were inoculated with 300 embryonated *T. canis* eggs. The 36 dogs (18 males, 18 females) with the highest mean egg per gram counts (EPGs) were stratified by EPGs within gender, and randomly assigned to one of three treatment groups (6 males and 6 females per group). The method of randomization was a randomization table generated using the SAS® statistical system (Cary, NC).

Dogs receiving the generic product (Group 1) and the pioneer product (Group 2) were treated once at 49 days post-inoculation. The dogs received a minimum dose of 2.27 mg/lb. of body weight (5mg/kg), in accordance with the labeled directions. The negative control group (Group 3) received no treatment. Masking was accomplished by separation of function. All individuals responsible for making study observations, including worm counts, were masked to the treatment groups. All dogs were necropsied 56 days post-inoculation. The gastrointestinal tract of each dog was removed and carefully examined to collect all *T. canis* worms. Recovered worms were counted, sexed, and preserved in 10% buffered formalin for retention.

Percent efficacy was calculated using the following formula:

$$\frac{\text{mean \# of parasites in control dogs} - \text{mean \# of parasites in treated dogs}}{\text{mean \# of parasites in control dogs}} \times 100 = \% \text{ efficacy}$$

Results and Analysis: Natural logarithmic worm counts were analyzed. The back-transformed mean worm counts for the generic and pioneer groups were 2.75 and 3.42, respectively. The back-transformed mean worm count for the negative control group was 18.32. Based on the mean worm counts, the percent efficacy of the generic product was 84.93% and the percent efficacy of the pioneer product was 81.35%.

The results from the pioneer and generic treated groups were statistically significantly different from the control group. The p-values were <0.0001 for each comparison. The statistical analysis of the data used a two-way analysis of variance with Treatment, Sex, and Treatment X Sex as factors in the statistical model. Block (Sex) was a random effect in the model. The 90% confidence interval lower and upper bounds were within ±10% of the improvement in the reference product over the placebo for the generic test product. This establishes the bioequivalence of the generic to the pioneer product.

Conclusions: Based on the results of this clinical end-point bioequivalence study, Wormexx™ flavored tablets are bioequivalent to D-Worm™ Dog Wormer Chewable Tablets for the treatment of roundworms in dogs.

B. A clinical end-point bioequivalence study was also conducted in dogs harboring natural infections of *T. canis*. However, the study design was inadequate for determining bioequivalence due to inadequate parasite infections in the experimental animals. Thus, no conclusions could be made.

2. Palatability Study:

Study Title: Trial to Compare the Palatability of Wormexx™ Tablets to D-Worm™ Dog Wormer Chewable Tablets in Dogs

Sponsor: Blue Ridge Pharmaceuticals, Inc.,
A subsidiary of Idexx Laboratories, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

Investigators/Study Locations:

Dr. Rodger Kleisch
Forest Oaks Animal Clinic
5310-H Liberty Road
Greensboro, NC 27406

Dr. Julie Packard
Bel-Aire Veterinary Hospital
7712 Kenmont Road
Greensboro, NC 27409

Objective: To compare the palatability of Wormexx™ Tablets to D-Worm™ Dog Wormer Chewable Tablets.

Study Summary: A total of 68 client-owned dogs (31 spayed females, 5 females, 26 castrated males, 6 males) ranging in age from 2 months to 11 years were enrolled, completed the study and were included in the data analysis. A total of 23 breeds and mixed-breeds were represented with body weights from 3.6 to 86.7 pounds. One-half of the dogs received the generic tablet on day 1, followed by the pioneer tablet on day 2 and the other half received the pioneer tablet on day 1, followed by the generic tablet on day 2. The sequence of tablet administration was assigned using a randomization table generated using the SAS statistical package (Cary, NC). The product was considered palatable if the owner recorded that the dog ate the tablet within three minutes of initial offering.

Results: Blue Ridge's Flavored Pyrantel Pamoate Tablets were palatable to 89.7% of the dogs and D-Worm Dog Wormer Chewable Tablets were palatable to 92.6% of the dogs. McNemar's test showed no statistical difference in palatability between the generic and pioneer product in palatability ($p=0.4795$).

Conclusions: Both Wormexx™ and D-Worm® Dog Wormer Chewable Tablets are palatable products and their palatability is not different, as seen in the results of this study.

3. HUMAN SAFETY:

Human Safety Relative to Food Consumption: None required as generic flavored pyrantel pamoate is intended for use only in dogs.

Human Safety Relative to Possession, Handling, and Administration: Labeling contains adequate caution/warning statements.

4. AGENCY CONCLUSIONS:

This is an Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal, Food, Drug and Cosmetic (FFD&C) Act.

Safety and effectiveness for this generic animal drug, Wormexx™, were established by demonstration of clinical end-point bioequivalence to the pioneer product, D-Worm™ Dog Wormer Chewable Tablets (NADA 139-191).

This generic product and the pioneer product have identical labeling indications for use in dogs. The route and method of administration of the two drugs are identical. Both drugs are administered orally. The generic and pioneer products contain the same active ingredient.

This ANADA satisfies the requirements of section 512 of the Act and demonstrates that Wormexx™ is safe and effective for its labeled indications, when used under the proposed conditions of use.

Attachments:

1. Generic Labeling:
   Bottle Labels for 22.7 & 113.5 mg tablets

2. Pioneer Labeling:
   Carton Labels for 22.7 & 113.5 mg tablets