Date of Approval: May 30, 2001

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

ANADA 200-302

Iverhart^{TM} Plus Flavored Chewables
(ivermectin and pyrantel pamoate) Flavored Tablets

For the prevention of canine heartworm (*Dirofilaria immitis*) disease and for the treatment and control of adult *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala*, and *Ancylostoma braziliense*.

Sponsored by:

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

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

ANADA:	200-302
Sponsor:	Blue Ridge Pharmaceuticals, Inc. 4249-105 Piedmont Parkway Greensboro, NC 27410
Generic Names:	Ivermectin and Pyrantel (as pamoate salt)
Trade Name:	Iverhart™ Plus
Dosage Form:	Flavored, Chewable Tablets
How Supplied:	Three dosage strengths are available for dogs of different weight classes. Each tablet size is packaged in blisters (6 tablets per card).
How Dispensed:	Rx
Amount of Active Ingredients:	Small tablet contains 68 mcg of ivermectin and 57 mg pyrantel as pyrantel pamoate; medium tablet contains 136 mcg of ivermectin and 114 mg pyrantel as pyrantel pamoate; large tablet contains 272 mcg of ivermectin and 227 mg pyrantel as pyrantel pamoate.
Route of Administration:	Oral
Species:	Canine
Labeled Dosage:	A minimum of 6 mcg of ivermectin and 5 mg of pyrantel pamoate/kg of body weight at monthly intervals.
Indications for Use:	Iverhart Plus is indicated for the prevention of canine heartworm (*Dirofilaria immitis*) disease and for the treatment and control of adult *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala*, and *Ancylostoma braziliense*.
Pioneer Product:	Heartgard® Plus, NADA 140-971, Merial Ltd.

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 ivermectin has been established by data contained in approved NADA 140-971, sponsored by Merial. The following studies establish the bioequivalence of the generic product, Iverhart Plus to the pioneer product, Heartgard Plus.

Clinical Endpoint Bioequivalence for Canine Heartworm Disease Prevention

The ivermectin portion of this ivermectin/pyrantel pamoate combination is known to provide the efficacy for the claim of the prevention of heartworm disease in dogs. The following study was conducted to determine the clinical endpoint bioequivalence of the two products, Iverhart Plus and Heartgard Plus for the claim of heartworm prevention in dogs. Blood-level bioequivalence studies were not required for this approval because blood levels of ivermectin at the approved dose in dogs are too low for accurate measurement throughout the pharmacokinetic profile of the drug.

Testing Facility: TRS Labs, Inc.
295 Research Drive
Athens, GA 30605

Investigator: Dr. John W. McCall

Objective: The objective of this study was to compare the clinical endpoint bioequivalence of Blue Ridge Pharmaceuticals' Iverhart Plus (ivermectin/pyrantel pamoate) to that of Merial's Heartgard Plus (ivermectin/pyrantel pamoate) for heartworm (*Dirofilaria immitis*) prevention in dogs. Thirty-six beagle dogs (18 males and 18 females), ranging between 6.3 and 8.8 months of age and weighing between 18.5 to 30.5 pounds, were obtained from a USDA licensed supplier. All dogs were inoculated subcutaneously with 50 *D. immitis* L3 larvae thirty days prior to the first treatment. All of the infective larvae were from the same source, of the same age, and handled in the same manner for this study. The dogs were stratified by weight and gender, and randomly assigned to one of three treatment groups (6 males and 6 females per group). Dogs receiving the generic product (Group 1) and the pioneer product (Group 2) were treated every thirty days, for a total of four treatments. The

dogs received a minimum dose of 6 mcg ivermectin and 5 mg pyrantel pamoate/kg of body weight. 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 119 days post-inoculation. The heart and lungs of each dog were removed and carefully examined to collect and count all *D. immitis* adults or macroscopic larvae.

Percent efficacy was calculated using the following formula:

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

Results and Conclusions: The worm counts for both treated groups (Iverhart Plus and Heartgard Plus) were 0 and the mean worm count for the negative control group was 24, with all control animals having heartworm infections. Thus, the reference product and the pioneer product were considered bioequivalent with efficacies of 100%, and no statistical analysis was conducted. Based on the results of this clinical end-point bioequivalency study, Blue Ridge Pharmaceuticals' Iverhart Plus is bioequivalent to Merial's Heartgard Plus for the prevention of heartworms in dogs.

Clinical Endpoint Bioequivalence for Gastrointestinal Nematodes.

The effective treatment of the canine gastrointestinal nematodes, for which this combination of drugs, in this dosage form, is approved is provided by the pyrantel pamoate portion of the ivermectin/pyrantel pamoate combination. Clinical data has demonstrated that *Toxocara canis*, the canine roundworm, is the most resistant to the effects of pyrantel pamoate, of those parasites, for which the pioneer product is approved, therefore, demonstration of clinical endpoint bioequivalence for this parasite is sufficient proof of efficacy for all the gastrointestinal nematode parasites found on the Iverhart Plus label.

Blood-level bioequivalence studies were not required for this approval because pyrantel pamoate is poorly absorbed from the G.I. Tract, and the systemic absorption of the drug is not necessary for the desired clinical effect. In the case of clinical endpoint anthelmintic studies, if the generic and pioneer products are both $\geq$ 90% efficacious, and there is a statistically significant difference in the worm burdens of the treated groups as compared to the controls, then bioequivalence is established.

Two studies were conducted to demonstrate the clinical endpoint bioequivalence of Heartgard Plus and Iverhart Plus for the treatment of adult roundworms (*Toxocara canis*) in dogs. Both studies were conducted by the same investigator, at the same facility, with the same objectives, and the same protocol design, but on different dates.

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

Investigator: Dr. Dwight Bowman

Objective: The objective of this study was to compare clinical endpoint bioequivalence of Blue Ridge Pharmaceuticals' Iverhart Plus (ivermectin/pyrantel pamoate) to that of Merial's Heartgard Plus (ivermectin/pyrantel pamoate) for the treatment of adult roundworms (*Toxocara canis*) in dogs.

Design: Thirty-six beagle dogs (18 males and 18 females) were obtained from a USDA licensed supplier. At inoculation, the dogs were 8 weeks of age and weighed between 4.55 and 8.05 pounds. All 36 dogs were inoculated orally with 300 embryonated *T. canis* eggs with the goal of obtaining 30 dogs positive for *T. canis* to include in the treatment groups. The 30 dogs (15 females, 15 males) with the highest mean egg per gram counts (EPGs) were stratified by EPGs within gender, and randomly assigned to one of three treatment groups (5 males and 5 females per group). 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 6 mcg ivermectin and 5 mg pyrantel pamoate/kg of body weight. 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 geometric means of the log transformed data.

- Study One Results and Conclusions: The mean worm counts for the Iverhart Plus and Heartgard Plus groups were 4.6 and 1.0, respectively. The mean worm count for the negative control group was 27.5. Based on the geometric means of the log transformed worm counts, the efficacy was 93.07% for Iverhart Plus and 97.62% for Heartgard Plus. However, one dog receiving Iverhart Plus had a worm count of 35. There is no definitive explanation for the apparent lack of efficacy in this animal; however, it is possible that the animal vomited the medication unobserved, and was not adequately treated, or carried an excessive initial parasite burden. Based on the results of this clinical end-point bioequivalency study, Blue Ridge Pharmaceuticals' Iverhart Plus is bioequivalent to Merial's Heartgard Plus for the treatment of roundworm infections in dogs.

- Study Two Results and Conclusions: The mean worm counts for the Iverhart Plus and Heartgard Plus groups were 0.6 and 1.8, respectively. The mean worm count for the untreated control group was 23.5. Based on the mean worm counts, the % efficacy of Iverhart Plus was 97.45% and the % efficacy of Heartgard Plus was 92.34%. Based on the results of this clinical end-point bioequivalency study,

Blue Ridge Pharmaceuticals' Iverhart Plus is bioequivalent to Merial's Heartgard Plus for the treatment of roundworms in dogs.

Palatability Study

In addition to clinical end-point bioequivalence studies, a comparative palatability study was also performed to show that Iverhart Plus has similar palatability to Heartgard Plus.

Investigators/Study Locations:

Dr. Rodger Kleisch	Dr. Julie Packard
Forest Oaks Animal Clinic	Bel-Aire Veterinary Hospital
5310-H Liberty Road	7712 Kenmont Road
Greensboro, NC 27406	Greensboro, NC 27409

Design: A total of 69 client-owned dogs (45 spayed females, 1 female, 19 castrated males, 4 males) ranging in age from 1.1 to 12.7 years were enrolled in the study and included in the data analysis (70 dogs were initially enrolled, but one case was excluded from the analysis due to protocol non-compliance). A total of 20 breeds and mixed-breeds were represented and the body weights ranged from 7.8 to 97.2 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 owner recorded if the dog ate the tablet within 3 minutes.

Results and Conclusions: Iverhart Plus was palatable to 95.7% of the dogs and Heartgard Plus was palatable to 100% of the dogs. McNemar's test showed no statistical difference in palatability between the generic and pioneer product in palatability ($p=0.0833$). Both Iverhart Plus and Heartgard Plus are palatable products.

3. HUMAN SAFETY:

Human Safety Relative to Food Consumption:

None required as Iverhart Plus 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, Iverhart Plus, were established by demonstration of clinical end-point bioequivalence to the pioneer product, Heartgard Plus, NADA 140-971.

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 ingredients.

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

Attachments:

1. Generic Labeling:

   Package Insert

   Blister Card Label for small, medium, and large tablets

   Box Label for small, medium, and large tablets

   Display Carton Label for small, medium, and large tablets

   Bulk Carton Label for small, medium, and large tablets

   Dispensing envelopes for bulk cards

   Reminder Stickers

2. Pioneer Labeling:

   Package Insert