Date of Approval: August 13, 2003

FREEDOM OF INFORMATION SUMMARY

Abbreviated New Animal Drug Application

ANADA 200-338

TRI-HEART Plus (ivermectin/pyrantel) Chewable 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*.

Sponsor:

Heska Corporation
1825 Sharp Point Drive
Fort Collins, Colorado 80525

1. GENERAL INFORMATION:

a.	File Number:	ANADA 200-338
b.	Sponsor:	Heska Corporation 1825 Sharp Point Drive Fort Collins, Colorado 80525 Drug Labeler Code: 063604
c.	Established Name:	Ivermectin/Pyrantel
d.	Proprietary Name:	TRI-HEART Plus (ivermectin/pyrantel) Chewable Tablets
e.	Dosage Form:	Chewable tablet
f.	How supplied:	TRI-HEART Plus is supplied in 3 dosage strengths for dogs of different weights. Each strength comes in packs of 6 chewable tablets.
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	Small tablet contains 68 mcg of ivermectin and 57 mg pyrantel (as pamoate salt); medium tablet contains 136 mcg of ivermectin and 114 mg pyrantel (as pamoate salt); large tablet contains 272 mcg of ivermectin and 227 mg pyrantel (as pamoate salt).
i.	Route of Administration:	Oral
j.	Species/class:	Canine
k.	Recommended Dosage:	A minimum of 6 mcg of ivermectin and 5 mg of pyrantel (as the pamoate salt)/kg of body weight at monthly intervals.
l.	Pharmacological Category:	parasiticide/anthelmintic

m. Indications: Prevents heartworm disease by eliminating the tissue stage of heartworm (*Dirofilaria immitis*) larvae for a month after infection and for the treatment and control of ascarids (*Toxocara canis, Toxascaris leonina*) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense*).

n. Pioneer Product: HEARTGARD Plus (ivermectin/pyrantel) Chewables, Merial Ltd., NADA 140-971.

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 Term Restoration Act, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product).

A Suitability Petition (98P-0927/CP1), requested by Heska Corporation, was granted to allow a generic copy of the pioneer's extruded chewable tablet with this compressed chewable tablet. The different dosage forms are similar and can be used interchangeably.

The sponsor has demonstrated *in vivo* bioequivalence, via clinical endpoint bioequivalence studies, of the generic product to the pioneer product to support the safety and efficacy of the generic product against *Dirofilaria immitis* (see Section 2.a.) and *Toxocara canis* (see Section 2.b.). Palatability was also evaluated in dogs and the study is reported below in Section 2.c.

The use of clinical endpoint bioequivalence studies instead of blood level bioequivalence for the ivermectin component was based on the fact that accurate measurement of blood levels was not possible for ivermectin at the approved dose over the entire pharmacokinetic profile.

The use of clinical endpoint bioequivalence studies for the pyrantel (as the pamoate salt) component is based on the poor absorption of pyrantel from the digestive tract, where it is locally active, and the poor correlation between blood levels and effectiveness.

a. Clinical Endpoint Bioequivalence for Canine Heartworm Disease Prevention

Two clinical endpoint bioequivalence studies were conducted against *Dirofilaria immitis* at the same facility, with the same objectives, and the same basic study design, but on different dates. The first study was invalidated due to inadequate infections in the control animals. The second study is described below.

Testing Facility: Professional Laboratory & Research Services, Inc.
Corapeake, North Carolina

Objective: The objective of this study was to determine the comparative efficacy of TRI-HEART Plus (ivermectin/pyrantel) chewable tablets and HEARTGARD Plus (ivermectin/pyrantel) chewables against developing stages of heartworm (*Dirofilaria immitis*) in dogs. *Dirofilaria immitis* was selected for testing because it is the parasite species on the pioneer product label which is eliminated by the ivermectin portion of this anthelmintic combination (ivermectin/pyrantel) product.

Design: Thirty beagle dogs (9 males, 21 females) ranging from approximately 8 to 10 months of age, and weighing between 17.5 and 25 pounds were artificially infected (*D. immitis* L3 larvae), ranked by weight within each sex, and randomly assigned to one of three treatment groups containing 7 females and 3 males. The dogs were treated 29 days after infection with TRI-HEART Plus chewable tablets (Group 2) or the pioneer product, HEARTGARD Plus chewables, (Group 3) at the recommended dosages. The negative control group (Group 1) received no treatment. The dogs were observed daily until sacrifice and necropsy 182 to 189 days post-infection. At necropsy, the heart and connecting vasculature of each dog were removed and the heartworms located in these organs were counted.

Results:

Table 1.

Group	Treatment	Geometric Mean Worm Count	Range	Percent Efficacy
1	None	48.2	37-60	N/A[1]
2	TRI-HEART Plus	0	N/A	100
3	HEARTGARD Plus	0	N/A	100

[1]N/A- not applicable

Percent efficacy was calculated using the following formula:

[(Geometric mean # of worms recovered from control dogs)-(Geometric mean # of worms recovered from treated dogs)]/(Geometric mean # of worms recovered from control dogs) x 100 = % efficacy

The generic product and the pioneer product were both 100% effective against developing stages of heartworms in dogs and no further statistical analysis was conducted.

Conclusion: The test product, TRI-HEART Plus Chewable Tablets, was found to be bioequivalent to the Reference Product, HEARTGARD Plus Chewables, with respect to claims for effectiveness in the prevention of infection with *Dirofilaria immitis*.

b. Clinical Endpoint Bioequivalence for Control of Gastrointestinal Nematodes

Testing Facility: Professional Laboratory & Research Services, Inc.
Corapeake, North Carolina

Objective: The objective of this study was to evaluate the comparative efficacy of Heska's TRI-HEART Plus (ivermectin/pyrantel) chewable tablets to that of Merial's HEARTGARD Plus (ivermectin/pyrantel) chewables for the treatment of adult roundworms (*Toxocara canis*) in dogs. *Toxocara canis* was selected for testing because it is the canine parasite species on the pioneer product label most resistant to the effects of pyrantel pamoate.

Design: Thirty puppies, naturally infected with *T. canis* (12 males, 18 females), of various breeds were enrolled in the study. The puppies were approximately 6 weeks of age or older, and weighed between 2.6 and 19.0 pounds at treatment. Weight ranked puppies were randomly assigned to one of three treatment groups of 10 puppies, each containing male and female pups, with the proportion of each sex dependent on body weight. Dogs receiving the generic product (Group 2) and the pioneer product (Group 3) were administered a single dose at the recommended dosage. The negative control group (Group 1) received no treatment. All dogs were observed daily until necropsy 7 days after treatment at which time the gastrointestinal tract of each dog was removed and carefully examined to collect and count all *T. canis* worms.

Results:

Table 2.

Group	Treatment	Geometric Mean Worm Count	Range	Percent Efficacy
1	None	11.9	2-30	N/A[1]
2	TRI-HEART Plus	0.9	0-6	92.4
3	HEARTGARD Plus	0.3	0-7	97.5

[1]N/A- not applicable

Percent efficacy was calculated using the following formula:

[(Geometric mean # of worms recovered from control dogs)-(Geometric mean # of worms recovered from treated dogs)]/(Geometric mean # of worms recovered from control dogs) x 100 = % efficacy.

Both generic and pioneer products resulted in a significant ($P<0.05$) reduction in roundworms compared to controls. Because both treatments resulted in greater than 90% efficacy, no further statistical analysis was undertaken.

Conclusion: The generic product, TRI-HEART Plus Chewable Tablets, was found to be bioequivalent to the pioneer product, HEARTGARD Plus Chewables, with respect to claims for effectiveness against *T. canis* in the canine.

c. **Palatability of Chewable Tablets**

Testing Facility: Summit Ridge Farms
Susquahanna, PA

Objective: The objective of this study was to compare the palatability of TRI-HEART Plus (ivermectin/pyrantel) chewable tablets to the palatability of the pioneer product, HEARTGARD Plus (ivermectin/pyrantel) chewables.

Design: A two-day crossover study was conducted with fifty adult beagle dogs (14 male and 36 female) ranging in age from approximately 1.5 to 7.5 years and weighing between 21 and 47 pounds. Dogs were ranked by body weight within each sex and randomly assigned to one of two treatment groups of 25 dogs each. Group 1 received one TRI-HEART Plus chewable tablet on the first day and one HEARTGARD Plus chewable on the second day. Group 2 received one HEARTGARD Plus chewable on the first day and one TRI-HEART Plus chewable tablet on the second day. The dogs were administered the treatments per label directions. Each dog was offered each treatment in a bowl placed on the cage floor and, after 2 minutes, the treatment was recorded as Consumed, Partially Consumed, or Not Consumed.

Results: Of the 50 dogs enrolled in the study, 45 readily consumed both products. One dog did not accept either product. Two dogs ate the HEARTGARD Plus chewable but did not eat the Tri-Heart Plus chewable tablet. Two dogs ate the TRI-HEART Plus chewable tablet but did not eat the HEARTGARD Plus chewable. McNemar's test showed no statistical difference in palatability between the generic and pioneer product ($P > 0.05$).

Conclusions: TRI-HEART Plus (ivermectin/pyrantel) chewable tablets and HEARTGARD Plus (ivermectin/pyrantel) chewables were found to be equally palatable to dogs.

3. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human Warnings are provided on the package label as follows:

Keep this and all drugs out of the reach of children. In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that TRI-HEART Plus Chewable Tablets, when used under the proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic animal drug, TRI-HEART Plus Chewable Tablets, were established by the demonstration of clinical end-point bioequivalence to the pioneer product, HEARTGARD Plus Chewables, NADA 140-971, sponsored by Merial, Ltd., for the parasites: *Dirofilaria immitis* and *Toxocara canis*. Palatability was also tested and found to be equivalent to that of the pioneer product.

5. ATTACHMENTS:

a. Generic Labeling:

Package Insert
Carton labels:
6 chewable tablets- Dogs up to 25 lbs.
6 chewable tablets- Dogs 26 to 59 lbs.
6 chewable tablets- Dogs 51 to 100 lbs.
Display units of 14 packs of 6 chewable tablets- Dogs up to 25 lbs.
Display units of 14 packs of 6 chewable tablets- Dogs 26 to 50 lbs.
Display units of 14 packs of 6 chewable tablets- Dogs 51 to 100 lbs.

b. Pioneer Labeling:

Package Insert
Carton label