I. GENERAL INFORMATION

A. File Number

NADA 140-971

B. Sponsor

Merck Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0914

C. Proprietary Name

Heartgard™ Plus)

D. Established Name

ivermectin; pyrantel (as pamoate salt)

E. Dosage Form

Ivermectin and pyrantel (as pamoate salt) are formulated in a meat-based chewable tablet. Three dosage strengths are available for dogs of different weight classes.

F. Dosage Regimen

HEARTGARD™ Plus is administered once monthly and provides a minimum of 6 mcg ivermectin per kg of body weight (2.72 mcg/lb) and a minimum of 5 mg pyrantel per kg of body weight (2.27 mg/lb) when given as follows:

Ivermectin	**Pyrantel**	**Dog Weight**
68 mcg	57 mg	Up to 11 kg (25 lb.)
136 mcg	114 mg	12 to 22 kg (26 to 50 lb.)
272 mcg	227 mg	23 to 45 kg (51 to 100 lb.)

Dogs heavier than 45 kg (100 lb.) are administered the appropriate combination of these chewable tablets.

G. Route of Administration

HEARTGARD™ Plus is administered orally at monthly intervals during the mosquito (vector for *D. immitis*) season.

H. Indication

For use in dogs: Ivermectin [to prevent canine heartworm disease by eliminating the tissue larval stages of *Dirofilaria immitis* for a month (30 days) after infection], and Pyrante pamoate (for the treatment and control of adult *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala* and *Ancylostoma braziliense*).

I. Effect of Supplement

This supplement expands the indications to include the treatment and control of adult hookworms (*Ancylostoma braziliense*).

II. EFFECTIVENESS

A. Dose Establishment

No additional dose establishment work was required. The minimum target doses of ivermectin (6 mcg/kg body weight) and pyrantel pamoate (5mg/kg) were established previously. The Freedom of Information Summary for the Heartgard®-30 chewables (Merck's NADA 140-886) application can be referenced to support the dose of ivermectin against the developing stages of heartworm. The Freedom of Information Summary for the Heartgard®-30 Plus chewables (Merck's NADA 140-971) application can be referenced to support the dose of pyrantel pamoate against the developing stages of hookworm (See FOI dated January 15, 1993).

B. Dose Confirmation

Two dose confirmation studies (Trials ASR #14326 and ASR #14543) were conducted to evaluate the effectiveness of HEARTGARD™ Plus in the removal and control of the adult hookworm, *A. braziliense.*

Trial ASR 14326 was conducted by Dr. John McCall at TRS Laboratories in Athens, Georgia. The trial used nine male and nine female purpose-bred beagles, 3.6 to 3.7 months old, and weighing 3.45 to 5.70 kg. Dogs were individually caged and were inoculated orally with approximately 400 infective larvae (L3) of *A. braziliense* 27 days before the day of treatment. Fecal flotation examinations conducted on the day before treatment confirmed infection with *A. braziliense*.

Pairs were formed by sex and body weight on the day before treatment; the ninth pair consisted of the lightest male and the lightest female. Within pairs, dogs were randomly allocated to an untreated control group or to treatment with HEARTGARD™Plus once, according to label directions (*i.e.*, dogs received ivermectin at the dosage of at least 6 mcg/kg and pyrantel as pamoate salt at the dosage of at least 5 mg/kg).

The dogs were examined at necropsy on Day 7, and collected worms were identified, counted and preserved. All nine control dogs had *A. braziliense* worms (geometric mean = 275.4 worms; range = 104 to 384). One dog treated with HEARTGARD™ Plus had one female *A. braziliense*. The efficacy of HEARTGARD™ Plus was calculated as 99.97% relative to the control group geometric mean. The difference between treatment groups was highly significant ($p<0.001$, by a *t*-test for means with equal variances).

Trial ASR 14543 was conducted by Dr. Bruce Kunkle at the Merck Farm in Fulton, Missouri. The trial used eight male and eight female beagles, approximately 6 months old, and weighing 9.3 to 14.4 kg. The animals were determined to be free of helminths on Day -29 by a fecal flotation technique. Dogs were individually caged and were inoculated orally with approximately 300 infective larvae (L3) of

A. braziliense 28 days before the day of treatment. Fecal flotation examinations conducted on the day before treatment confirmed the infection.

Within pairs formed by sex and body weight on the day before treatment, dogs were randomly allocated to an untreated control group or to treatment HEARTGARD™ Plus once, according to label directions.
Dogs were observed for retention of the dose. Three dogs vomited the chewable or a portion thereof, and in each case, the chewable that had been vomited was re-administered. Vomiting did not recur in animals who were administered the chewables. This reaction is considered a response to tablet administration and not treatment.

Dogs were examined at necropsy on Day 7, and collected worms were identified, counted and preserved. All eight control dogs had *A. braziliense* worms (geometric mean = 137.1 worms; range = 59 to 262). None of the dogs treated with HEARTGARD™ Plus had hookworms. No adverse reactions to treatment were reported. The difference between treatment groups was highly significant ($p<0.001$, by a *t*-test for means with unequal variances). These studies demonstrate 100% efficacy of HEARTGARD™ Plus against *A. braziliense*.

C. Clinical Field Trials

Five clinical trials were originally conducted under NADA 140-971 to confirm the efficacy, safety and acceptability of the chewable formulation of HEARTGARD™ Plus (ivermectin/pyrantel) against heartworms, hookworms and ascarids of dogs. Safety and efficacy data for hookworms was extracted to support the label change for this supplement. Various breeds of dogs, 6 months to 14 years of age, and ranging from 2.6 to 68 kg in body weight were used. Animals were administered HEARTGARD™ Plus chewables at monthly intervals (5 months). Fecal exams were conducted prior to each treatment and within one month following the last treatment. Efficacy was demonstrated at 100% in each of the trials (See table 1 below).

TABLE 1

Investigator/Location	**Trial #**	**No. of Animals (+) Before Treatment**	**No. of Animals (-) After the Final Treatment**	**% Efficacy**
Acre/FL	#12779	4	4	100%
Coleman/FL	#12780	4	4	100%
Currin/NC	#12781	7	7	100%
Weiner/GA	#12906	2	1	100%[1]
Lange/TN	#12907	3	3	100%
Total		20	19	

[1]One of two animals diagnosed with hookworms prior to study initiation died prior to conducting the final fecal exam. The efficacy of Heartgard-30® plus for the remaining animal (1) was 100%.

D. Supportive Clinical Field Trials

Three clinical trials were conducted following the approval of the NADA to confirm the efficacy, safety and acceptability of the chewable formulation of HEARTGARD™ Plus (ivermectin/pyrantel) against heartworms, hookworms and ascarids of dogs. Safety and efficacy data for hookworms was extracted to support the label change for this supplement. Various breeds of dogs, 1 month to 13 years of age, and ranging from 3 to 70 kg in body weight were used. Animals were administered HEARTGARD™ plus chewables at monthly intervals (#13628: 9 months, #13647 and #13648: 3 months). Fecal exams were conducted prior to the start of the trial for each trial. Additional fecals were conducted at 5 months after the first treatment and at 0 to 28 days after the final treatment (#13628) or on the day of treatment to 39 days following the last treatment (#13647 and #13648). Each animal was observed up to eight hours following each dose of HEARTGARD™ Plus. There were 15 reported cases of diarrhea and 8 reported cases of vomiting which occurred within 24 hours of tablet administration. While these reported cases of vomiting and diarrhea were considered treatment related, both are already listed in the adverse reactions section of the approved product label. The average efficacy of the trials was demonstrated to be 92% (See table 2 below).

TABLE 2

Investigator/Location	**Trial #**	**No. of Animals (+) Before Treatment**	**No. of Animals (-) After The Final Treatment**
Labarthe/Brazil	#13628	32	26
McArthur/GA	#13647	26	25
Clekis/SC	#13648	24	24

Conclusion: Based upon the 100% efficacy demonstrated in the dose confirmation studies (2), the 100% efficacy in the clinical field trials (5), and the supportive clinical field trials (3), this data is adequate to support the expansion of the hookworm claim (*A. braziliense*). The enrolled clinical field trial cases are applicable to this additional hookworm claim based on the inability to distinguish hookworm species based on egg size. There are overlapping sizes among hookworm species and practitioners do not distinguish to differentiate species under typical veterinary clinical settings.

III. TARGET ANIMAL SAFETY

This supplemental NADA does not require re-evaluation of target animal safety data submitted in support of the initial NADA No. 140-971. Please refer to the original Freedom of Information Summary (NADA 140-971) for additional information on target animal safety studies.

IV. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental NADA. The drug is to be labeled for use in dogs, which are non-food animals.

V. AGENCY CONCLUSIONS

The data in support of this supplemental NADA application complies with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that HEARTGARD™ Plus, when used under the labeled conditions of use, is safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a category II change. This supplement provides for an additional claim for the removal and control of the adult hookworm, *A. braziliense*. This approval relied upon the safety and effectiveness data in the parent application and evaluation of new efficacy data submitted in the supplemental application.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (FF DCA), this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the additional adult hookworm claim (*A. braziliense*) for which the supplemental application was approved. This exclusivity period will expire three years from the date of the approval letter.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of hookworm and/or roundworm infection. In addition, professional expertise is required to determine the existence of heartworm infection, and then properly treat existing heartworm infection prior to starting treatment with HEARTGARD-30Plus in a prevention program.

VI. ATTACHMENTS

Veterinary insert

Summary of necropsy results (Trials ASR #14326 and ASR #14543)

Treatment Group	**ASR 14326 - Dog**	**ASR 14326 - Worm Count**	**ASR 14543 - Dog**	**ASR 14543 - Worm Count**
Untreated control	NK	355	39835	107
Untreated control	PE	270	39306	137
Untreated control	NA	104	39836	94
Untreated control	PS	378	36774	121
Untreated control	MJ	384	39274	200
Untreated control	TT	340	37493	262
Untreated control	MY	317	37722	241
Untreated control	PF	341	35843	59
Untreated control	RM	171		
Geometric mean[a]		275.44		137.14
HEARTGARD-30 Plus	NJ	0	39277	0
HEARTGARD-30 Plus	PT	0	39834	0
HEARTGARD-30 Plus	NI	0	35844	0
HEARTGARD-30 Plus	RL	0	39838	0
HEARTGARD-30 Plus	RV	0	37495	0
HEARTGARD-30 Plus	RU	0	35841	0
HEARTGARD-30 Plus	PI	1	37491	0
HEARTGARD-30 Plus	PH	0	34592	0
HEARTGARD-30 Plus	PJ	0		
Geometric Mean[a]		0.08		0.0
Percent Efficacy (relative to control)		99.97%		100.0%

[a]Retransformed from ln (count + 1)

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.