I. GENERAL INFORMATION

A. File Number

NADA 140-971

B. Sponsor

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

C. Proprietary Name

HEARTGARD-30® Plus

D. Established Name

ivermectin and 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. Dispensing Status

Prescription

G. Dosage Regimen

HEARTGARD-30® Plus chewable tablets are administered once monthly and provide 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	2.27 to 11 kg (5 to 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.

H. Route of Administration

HEARTGARD-30® Plus is administered orally at monthly intervals during the mosquito (vector for *D. immitis*) season.

I. 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), Pyrantel pamoate (for the treatment and control of adult *Toxocara canis, Toxascaris leonina, Ancylostoma caninum* and *Uncinaria stenocephala*).

II. EFFECTIVENESS

Adequate data support the efficacy of ivermectin at a dose rate of 6 mcg/kg body weight in preventing the development of heartworm larvae in dogs. The New Animal Drug Application for HEARTGARD-30® Plus contains data demonstrating that it is equivalent to HEARTGARD-30® Chewables with respect to ivermectin. 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.

Data from three pivotal dose determination and three pivotal dose confirmation trials, submitted to this combination NADA, demonstrate that the two new sources of pyrantel used in the formulation (Farmos Group, Ltd and Cosmos S.p.A.), at a dose rate of 5 mg/kg, are effective for the labeled indications for use.

Two pivotal dose confirmation studies with HEARTGARD-30® Plus were conducted against *D. immitis*. The percent control in both studies was 100% indicating that the pyrantel does not interfere with the efficacy of the ivermectin in the combination. In the three pivotal dose confirmation studies against the intestinal parasites, the efficacy of HEARTGARD-30® Plus was not statistically different than that of pyrantel, indicating that the ivermectin does not interfere with the efficacy of the pyrantel in the combination.

A. Bioequivalence Study

A bioequivalence trial (Table 1, Trial #12664) was conducted to show that HEARTGARD- 30® Chewables (Merck's NADA 140-886) are bioequivalent to HEARTGARD-30® Plus, with respect to ivermectin. The study used a two-period crossover design. Eighteen non- pregnant female dogs received each of two treatments: HEARTGARD-30® Chewables containing tritiated ivermectin to provide a dose rate of 6 mcg/kg body weight, or HEARTGARD-30® Plus to provide the same dose of tritiated ivermectin and pyrantel at 5 mg/kg body weight.

Blood was collected at various intervals after treatment on Day 0 (Period I) and Day 28 (Period II). Plasma was assayed for radioactivity, and results were calculated based on ng- equivalents of ivermectin per mL of plasma.

Statistical analysis of area under the curve (AUC), peak ivermectin concentration (Cmax) and time to peak ivermectin concentration (Tmax) used an analysis of variance for a 2- period crossover design. Plasma ivermectin concentration data were analyzed using a repeated measures analysis of variance.

Confidence intervals (90%) were constructed for the true mean values for HEARTGARD-30® Plus.

HEARTGARD-30® Plus was equivalent to the HEARTGARD-30® Chewable formulation with respect to the bioavailability of ivermectin. The AUC and Cmax were not statistically significantly different for the two formulations ($p>.20$).

Confidence intervals confirmed that the AUC and Cmax for HEARTGARD-30® Plus fell within 10% and 15%, respectively, of the HEARTGARD-30® Chewable formulation. The Tmax was longer by about 2.5 hours for HEARTGARD-30® Plus, but since the formulation is intended for monthly use, this difference is of no clinical significance.

B. Dose Selection

1. Pivotal Dose Determination Studies

Three well controlled dose determination trials (Table 1, Trial #'s 12665, 12489, and 12444) were conducted against induced and/or natural infections of ascarids and/or hookworms using pyrantel formulated in the vehicle for HEARTGARD-30® Plus. Trial #12665 was conducted against induced infections of *Ancylostoma caninum, Uncinaria stenocephala, Toxocara canis ,* and *Toxascaris leonina* ; Trial #12489 against natural infections of *T. canis* , and Trial #12444 against natural infections of *T. canis* and induced infections of *A. caninum* . Four dogs within each replicate were randomly allocated to one of four treatments and dosed orally with vehicle only or with pyrantel at a dose rate of 2.5, 5 or 10 mg/kg body weight. Treatments were tailored to the weight of the individual animal. Dogs were individually penned following treatment. At necropsy 7 days after treatment, nematodes were recovered from the intestinal tract, counted, and identified according to species and stage of development. The total fecal output from each dog was collected daily on approximately Days -1 to 7, and nematode eggs and worms recovered were counted at specific time points.

Geometric mean parasite counts at necropsy were calculated for each group for each parasite using log (count +1). In combining data on a single parasite from 2 or more trials, overall treatment group geometric means were calculated as the geometric mean of the trial geometric means, weighting trials equally. The transformed adult *T. canis* counts were analyzed using an analysis of variance and contrasts to explore dose-response models.

The following table shows the percent efficacy against adult *T. canis, T. leonina, A. caninum* and *U. stenocephala* from the three trials:

	2.5 mg/kg	**5.0 mg/kg**	**10 mg/kg**
T. canis	70.0	94.2	90.7
T. leonina	85.6	92.0	97.6
A. caninum	88.6	93.8	93.3
U. stenocephala	100	93.5	98.7

For all parasites, counts in the control group were statistically significantly higher than those in the pyrantel groups ($p<.01$). In most of the studies, there were no statistically significant differences between pyrantel treated groups. However, for *T. canis, T. leonina* , and *A. caninum* , the 2.5 mg/kg dose groups had less than the required 90% efficacy. Based on the results of these studies, a dose of 5.0 mg/kg was selected as effective. Table 2 shows the percent efficacy of the selected pyrantel dose (5 mg/kg) in the individual trials.

2. Pivotal Dose Confirmation Trials

Two well controlled studies (Table 1, #'s 12589 and 12590) were conducted to demonstrate the efficacy of HEARTGARD-30® Plus against the developing stages of heartworms, and three separate studies (Table 1, #'s 12591, 12592 and 13095) confirmed the efficacy against hookworms and/or ascarids. All trials used the proposed market formulation of HEARTGARD-30® Plus or single component chewable tablets based on the HEARTGARD-30® Plus vehicle.

a. **Heartworm**
Two studies (Table 1, #'s 12589 and 12590) were conducted using induced infections of *Dirofilaria immitis* . Each study used 32 heartworm-free Beagles (16 of each sex). These studies evaluated the components of the combination as well as the combination product. Eight replicates of 4 dogs each were formed, based on sex and weight. Within replicates of 4 dogs each were formed, based on sex and weight. Within replicates, dogs were randomly allocated to one of four treatments: (1) vehicle, (2) ivermectin, (3) pyrantel, or (4) HEARTGARD-30® Plus. Ivermectin and pyrantel were administered at 6 mcg/kg and 5 mg/kg body weight, respectively. All treatments were incorporated into the vehicle of the proposed commercial formulation, tailored to the weight of each animal and given once orally.

Dogs were infected with *D. immitis* larvae and treated 30 days later. Approximately 5 to 6 months after challenge with heartworm larvae, dogs were euthanized and examined for the presence of heartworms. HEARTGARD-30® Plus was shown to be 100% effective against 30-day-old larvae of *D. immitis* . All animals in the control and pyrantel groups were infected.

b. **Intestinal Parasites**
Three well controlled trials (Table 1, #'s 12591, 12592, and 13095) were conducted using induced parasitic infections of Ancylostoma caninum, Uncinaria stenocephala, and Toxascaris leonina and natural infections of Toxocara canis and Ancylostoma caninum. Ivermectin and pyrantel were given at 6 mcg and 5 mg/kg body weight, respectively. Trial #12591 included 36 dogs with natural *T. canis* and *A. caninum* infections. Trial #12592 included 32 dogs with induced infections of *T. leonina, A. caninum*, and *U. stenocephala* . In these efficacy studies, dogs within each of 8 replicates were randomly allocated to receive (1) vehicle, (2) ivermectin, (3) pyrantel or (4) HEARTGARD-30® Plus in the proposed market formulation. The remaining dose confirmation study (# 13095) was conducted with 16 dogs to demonstrate the efficacy of HEARTGARD-30® Plus against induced infections of the two hookworm species. Dogs within 8 replicates were randomly allocated to receive (1) vehicle or (2) HEARTGARD-30® Plus.

In all trials, dogs were treated orally once on Day 0 and necropsied on Day 7 at which time worms in the intestinal tract were collected, counted and identified according to species and stage of development. Geometric mean counts at necropsy were calculated for each group for each parasite,

using log (count +1). Overall treatment group means weighted trials equally.

Efficacy of pyrantel at 5 mg/kg against adult *T. canis, T. leonina, A. caninum* , and *U. stenocephala* is presented in Table 2. In each case, the mean worm count for HEARTGARD-30® Plus was significantly lower ($p<.01$) than the control mean. In the component efficacy studies, the efficacy of HEARTGARD-30® Plus was generally significantly higher ($p<.02$) than the ivermectin-treated group, but not significantly different from the pyrantel-treated group within individual studies ($p>.20$).

In study #12591, one dog in group 3 and one dog in group 4 died from parvovirus during the terminal part of the study (days 5 to 7). The reduction in efficacy against *T. canis* seen in this study (<90%) was possibly due to a change in intestinal transit time associated with the infection.

3. Corroborative Dose Confirmation Trials

   a. **Heartworm**
   One controlled study (Table 1, #12767) was conducted using an induced infection of Dirofilaria immitis in 32 heartworm-free Beagles (16 of each sex). The dogs were formed into 8 replicates of 4 dogs each by weight and sex. Within replicates, dogs were randomly allocated to one of four treatments- (1) vehicle, (2) HEARTGARD-30® Plus, (3) pyrantel, or (4) HEARTGARD-30® Plus and pyrantel (due to improper labeling instructions, dogs in the second treatment group received a combination chewable tablet instead of an ivermectin chewable tablet alone and dogs in the fourth treatment group received a combination chewable tablet and a pyrantel chewable tablet instead of the combination chewable tablet alone). All treatments were given orally 30 days after infection with *D. immitis* . Five months after challenge with heartworm larvae, dogs were euthanized and examined for the presence of heartworms. HEARTGARD-30® Plus was shown to be 100% effective against 30-day old larvae of *D. immitis* . All animals in the control and pyrantel groups were infected.

   b. **Intestinal Parasites**
   One controlled study (Table 1, #12765) was conducted in 36 dogs using natural infections of *Toxocara canis* and *Ancylostoma caninum* while a second study (Table 1, #12766) was conducted in 32 dogs using induced infections of *Toxascaris leonina, Uncinaria stenocephala* and *Ancylostoma caninum* . The dogs in both studies were dosed as in the corroborative heartworm study due to the same labeling error. The percent control of HEARTGARD-30® Plus was 91.6% against *T. canis* , 97.6% against *T. leonina* , and 100% against *U. stenocephala* . The *A. caninum* infections did not take in either study. Two dogs in group 2 died from parvovirus infection 2 to 4 days following treatment.

C. Clinical Field Trials

Eight clinical field trials (see Table 1) were conducted with 8 investigators in 6 geographic locations using client-owned dogs to establish the safety, efficacy and acceptability of HEARTGARD-30® Plus under field use conditions. Dogs were maintained in their normal environments and were subject to concomitant therapy generally administered to dogs under veterinary care. Prior to being placed on trial, dogs > 6 months old were shown to be heartworm-free by means of a microfilariae test (Knott or Difil®, EVSCO). Fecal examinations for intestinal tract nematodes were conducted prior to treatment and at various intervals during the trials.

For each 3 dogs that received HEARTGARD-30® Plus, 1 dog (control group) received HEARTGARD-30® swallow tablets and pyrantel pamoate (NEMEX®/Pfizer, U.S. or PYR-A-PAM 2/Rotar FIB, London). All medications were given monthly for 5 to 7 months. HEARTGARD-30® Plus was dosed to provide ivermectin at a minimum of 6 mcg/kg body weight and pyrantel at a minimum of 5 mg/kg body weight. In the positive control group, pyrantel and ivermectin were dosed according to the manufacturers' recommendations.

Owners recorded acceptability of the combination chewable tablet and any concurrent therapy, reactions or observations during the trial. No owner had more than 4 dogs on trial. Clinical trial reports were compiled from owner's and investigator's recorded observations.

A summary of the eight field trials conducted is shown in Table 3. In all, 323 animals were treated with HEARTGARD-30® Plus, and 107 were included in the control group. The trials included 280 female and 150 male dogs aged 6 months to 14 years and weighing from 1.6 to 68 kg. These animals represented 122 breeds, varieties or types, including Collies or Collie crosses.

Although approximately 85-90% of the dogs in the field trials received all scheduled monthly doses, fifty-five dogs did not complete the trials because of lack of owner compliance (#30), death/illness due to unrelated causes (#14), or loss of dog or contact with owner (#11).

HEARTGARD-30® Plus was shown to be effective for the treatment and control of hookworms and ascarids under field use conditions. No hookworm eggs were detected in 94.7% of dogs and no ascarid eggs were detected in 99.0% of dogs. HEARTGARD-30® Plus also was shown to be completely effective in preventing the development of *D. immitis* . HEARTGARD-30® Plus was consumed with an overall acceptability of 97%. Four dogs accepted the chewable tablet after it was broken or crumbled, 2 needed more than 1 attempt before they would accept it, 2 accepted the chewable tablet with some hesitation, and 2 were force-fed.

A number of vaccines, antibiotics, flea control preparations (dips, collars, mists, shampoos, etc.), steroids, vitamins, cestocides, antiinflammatories, anesthetics, tranquilizers, ophthalmic medications and hormone preparations were administered during the course of the studies. No adverse reactions occurred with the concomitant use of these products, demonstrating the safety of HEARTGARD-30® Plus when used under field conditions concurrent with commonly used veterinary products.

A number of clinical observations were recorded for both treatment groups during the trial. The incidence of vomiting and diarrhea, the most commonly observed clinical conditions, was low (1.1% of administered doses).

D. Controlled Clinical Acceptability

The acceptability of 18 to 24-month-old HEARTGARD-30® Plus chewable tablets was compared to that of < 3-month-old chewable tablets (Table 1, #13713). Each of 60 dogs received one of each age chewable tablet with an interval of 14 days. Acceptability was evaluated by the owners as 1: Dog accepted the chewable tablet or 2: Rejected. The average acceptability score for both groups (new and older HEARTGARD-30® Plus chewable tablets) was 1.0. The acceptability of the 18 to 24-month-old and the < 3-month- old chewable tablets was equivalent.

E. Conclusions from Drug Effectiveness Studies

The results of these efficacy trials demonstrate that HEARTGARD-30® Plus prevents the development of *D. immitis* larvae and is effective for the treatment and control of infections of *A. caninum, U. stenocephala, T. canis* and *T. leonina*. Results of clinical trials confirm that HEARTGARD-30® Plus is safe and effective for use under field conditions in the presence of concomitant standard veterinary therapy. HEARTGARD-30® Plus was consumed with an overall acceptability of 97% in the clinical field trials.

III. TARGET ANIMAL SAFETY

In target animal and clinical safety studies, ivermectin has been shown to have a wide margin of safety in dogs at the recommended heartworm-preventive dose. This is supported by field use of the product in several countries worldwide. The bioequivalence study (Table 1, # 12664) demonstrated that HEARTGARD-30® Plus and HEARTGARD-30® Chewables are equivalent with respect to ivermectin. This allows reference to the ivermectin safety data presented in the Freedom of Information Summary for HEARTGARD-30® Chewables (Merck's NADA 140-886).

Two pivotal safety studies (Tablet 1, #'s 12666 and 12932) and one corroborative safety study (#12663) were conducted to determine the safety in the target animal of the two new sources of pyrantel (Farmos Group, Ltd and Cosmos S.p.A.) used in the HEARTGARD-30® Plus formulation. These included pup tolerance (#12932), reproductive safety (#12666) and repeated treatment studies (#12663). The results of these trials confirm that HEARTGARD-30® Plus is safe for use in most classes of dogs including breeding animals and pups six weeks of age and older.

A. Pup Safety

A study was conducted in Beagles, aged 38-49 days, to demonstrate safety in pups. Thirty-two pups were treated at 1, 3 or 5X the target dose of HEARTGARD-30® Plus given on 3 successive days and repeated 3 times within a 30-day period. Replicates of 4 pups from each of 8 litters were formed.

Within replicates, dogs were randomly allocated to 4 treatment groups: vehicle, ivermectin/pyrantel (1X use level, i.e., 6 mcg ivermectin and 5 mg pyrantel/kg body weight, respectively), ivermectin/pyrantel (3X use level, i.e., 18 mcg ivermectin and 15 mg pyrantel/kg body weight, respectively), or ivermectin/pyrantel (5X use level, i.e., 30 mcg ivermectin and 25 mg pyrantel/kg body weight, respectively). Treatments, based on body weights obtained on Days -3, 11 and 25, were given on Days 0, 1, 2, 14, 15, 16, 28, 29 and 30. Hematology, serum chemistry, fecal analyses and clinical observations were performed. All animals in the control and high-dose groups were necropsied on Day 35 or 36, and tissues were examined for gross and microscopic pathology.

Clinical pathology and physical examination data were analyzed by analysis of variance or covariance for a repeated measures design.

Initial and terminal physical examinations did not reveal any treatment related effects. Some dehydration was observed in animals of all groups and was considered to be related to weaning and adapting to solid feed and individual housing. Random vomiting was reported in all groups and was usually of one day duration.

Clinical pathology results indicated changes in the treated animals in the following parameters: calcium, creatinine, MCHC, phosphorus and WBC. There were also treatment effects seen in eosinophils, platelets, prothrombin time, albumin, BUN, protein, potassium and phosphorus. None of these differences were considered to be biologically or clinically significant. There were no changes in temperature, weight gain or changes in heart rate and no differences between groups in fecal bilirubin, occult blood or microscopic examinations. On necropsy there were no treatment related lesions. Occasional incidental findings in control and treated animals included agonal congestion in lymph nodes and thymus, splenic capsule scars, focal areas of pneumonia and normal but small thyroid lobes. On histopathology there were no drug related microscopic lesions observed in the tissues examined. Microscopic findings were either agonal or typical of common background findings in dogs of this age and breed.

B. Reproductive Safety

A trial (Table 1, #12666) was conducted to evaluate safety of HEARTGARD-30® Plus in breeding male and female dogs.

Thirty-six bitches were paired by weight and randomly allocated to one of two treatment groups within pairs. Sixteen males, selected on the basis of a normal semen analysis, were paired based on pretreatment sperm counts and were randomly allocated within pairs to treatment. Treatment consisted of either HEARTGARD-30® Plus at 3X the target use level (a total of 18 mcg ivermectin and 15 mg pyrantel/kg body weight) or vehicle chewable tablet administered orally. Males were dosed weekly through Day 63, then daily from Day 68 through breeding. Females received 8 to 14 weekly doses prior to breeding, then were dosed daily through the first half of pregnancy and weekly for the remainder of gestation through weaning.

Semen analysis and body weights were evaluated weekly during the trial. Physical examinations were performed prior to treatment and at the conclusion of the trial. Each treatment group of studs was assigned to a breeding sequence, and bitches were allocated to the appropriate stud based on onset of estrus. Each bitch had two breeding opportunities. Breeding began on the final day of semen collection (Day 85).

Fertility, whelping and weaning indices were calculated, and pups that were born dead or died during the course of the study were necropsied. Data on semen characteristics; stud, bitch and pup weights; proportion of pups weaned and percent with abnormalities were analyzed with the appropriate analysis of variance or covariance. Litter size was analyzed using an exact randomization procedure.

HEARTGARD-30® Plus, given orally at 3X the target dose through one reproductive cycle, was found to have no effect on semen evaluations in terms of total sperm count, speed of progression, motility or pH. Sperm morphology and semen color in both test and vehicle treatment groups were normal.

The following table shows the breeding indices from both groups:

	#Whelped/#Bred (Conception Rate)	**Mean Litter Size**	**Weaning Percent**
Vehicle	8/12 (66.7%)	6.0	91.1%
Heartgard-30® Plus	11/12 (91.7%)	5.5	84.2%

Four puppies in the vehicle-treated group died due to the following: 1 from an umbilical infection, 1 was crushed, 1 was rejected by the dam, and 1 was unable to nurse due to a cleft palate. Ten puppies died in the HEARTGARD-30® Plus-treated group due to the following: 4 were crushed, 1 was rejected, 1 was euthanized due to a congenital deformity, and 4 did not nurse. The treatment groups were not significantly different for litter size at birth or weaning ($p>1.0$). Congenital abnormalities were seen in 7 of 48 pups born in the vehicle control group (cleft palate, anasarca, runt, open fontanel, prognathia, harelip, and flat chest) and 5 of 61 pups born in the group treated at 3X HEARTGARD-30® Plus (missing kidney, gastroschisis, open fontanel, persistent pupillary membrane and kinked tail). The treatment groups were not significantly different for percent of pups with abnormalities ($p>2.0$). Types and incidence of malformations seen were not markedly different from those in the breeding colony and therefore were not attributed to treatment.

C. Corroborative Repeated Treatment Study

A study (Table 1, # 12663) was conducted to evaluate the toxic potential of repeated oral treatment with ivermectin alone or in combination with 2 levels of pyrantel. Six replicates of 4 Beagles each were allocated to 4 treatment groups-(1) vehicle only, (2) ivermectin (6 mcg/kg), (3) ivermectin/pyrantel (6 mcg and 5 mg/kg, respectively), and (4) ivermectin/2X pyrantel (6 mcg/kg ivermectin, 10 mg/kg pyrantel). All medications were administered daily for 5 consecutive days. Dogs were evaluated by a physical examination prior to the study and by general observations through Day 4 and again on Day 7. On Days 0,

1, 4, and 7 blood was drawn and urine collected for CBC, serum chemistry, and urine analysis. At the end of the trial on Day 7, 3 dogs treated with ivermectin/2X pyrantel were euthanized, necropsied and examined for any gross or histopathologic changes.

Ivermectin alone or in the presence of up to 2 times the target dose of pyrantel did not cause any drug-related adverse physical or clinical signs in this study. There were no gross lesions at necropsy or histomorphologic changes on light microscopic examination of tissues following necropsy.

D. Target Animal Safety Conclusions

HEARTGARD-30® Plus has a wide margin of safety when administered repeatedly at elevated doses to dogs including 6-week-old pups and breeding studs and bitches.

IV. HUMAN SAFETY

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

Human safety relative to possession, handling, and administration: Labeling contains adequate caution/warning statements.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and 21 CFR 514.111 of the regulations. It demonstrates that HEARTGARD-30® Plus Chewable tablets, when used under the labeled conditions of use, are safe and effective.

Section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act provides a three year period of exclusivity to this original new animal drug application because new clinical or field investigations (other than bioequivalence or residue studies) essential to this approval were conducted or sponsored by the applicant.

Compliance with 21 CFR 514.1 (b)(8)(v) and the Center's Drug Combination Guideline:

HEARTGARD-30® Plus is a 2-way combination of ivermectin and pyrantel pamoate. The sponsor conducted adequate and well controlled safety and effectiveness studies, including dose determination and field studies, that demonstrate the source of pyrantel pamoate used in the formulation of HEARTGARD-30® Plus is safe and effective for the labeled indications for use.

The sponsor also conducted 2 pivotal dose confirmation studies with HEARTGARD-30® Plus against *D. immitis* . The percent control in both studies was 100% indicating that the pyrantel does not interfere with the efficacy of the ivermectin in the combination. In three pivotal dose confirmation studies against the

intestinal parasites, the efficacy of HEARTGARD-30® Plus was not statistically different than that of the pyrantel, indicating that the ivermectin does not interfere with the efficacy of the pyrantel in the combination.

The data submitted in the NADA demonstrate that the combination of ivermectin and pyrantel is superior to ivermectin alone or pyrantel alone for the labeled indications for use.

The drug is restricted to use by or on the order of a licensed veterinarian as knowledge of veterinary parasitology is needed for the safe use, monitoring and detection of possible adverse reactions with this drug.

TABLE 1: IDENTIFICATION OF INVESTIGATORS AND TRIAL LOCATION FOR HEARTGARD-30® Plus EFFECTIVENESS, SAFETY AND CLINICAL TRIALS

Trial	Investigator	Location	Objective
12664	Dr. R. Jeffcoat Dr. E. Cheung	Research Triangle Institute Research Triangle Park, NC	Bioequivalence
12665	Dr. S. Rubin Dr. L. Polley	Univ of Saskatchewan Saskatchewan, Canada	Dose determination, pyrantel
12489	Dr. D. Jacobs	Royal Veterinary College Hertsfordshire, U.K.	Dose determination, pyrantel
12444	Dr. F. Horchner	University of Berlin Berlin, Germany	Dose determination, pyrantel
12589	Dr. J. McCall	TRS Laboratories Athens, GA	Dose confirmation Heartworms
12590	Dr. K. Acre	Acre Farm Eustis, FL	Dose confirmation Heartworms
12591	Dr. E. Robertson	Univ of Georgia Athens, GA	Dose confirmation Intestinal parasites
12592	Dr. E. Robertson	Univ of Georgia Athens, GA	Dose confirmation Intestinal parasites
13095	Dr. G. Schad	Univ of Pennsylvania Philadelphia, PA	Dose confirmation Intestinal parasites
12767	Dr. K. Todd Dr. A. Paul	Univ of Illinois Urbana, IL	Corroborative Dose confirmation Heartworms
12765	Dr. K. Todd Dr. A. Paul	Univ of Illinois Urbana, IL	Corroborative Dose confirmation Intestinal parasites
12766	Dr. K. Todd Dr. A. Paul	Univ. of Illinois Urbana, IL	Corroborative Dose confirmation Intestinal parasites
12774	Dr. R. Blakely	Central Hospital for Animals Carterville, IL	Controlled clinical/efficacy/field safety/acceptability
12779	Dr. K. Acre	Howell Branch Animal Hosp. Winter Park, FL	Controlled clinical/efficacy/ field safety/acceptability
12780	Dr. M. Coleman	Suburban Animal Hospital Gainesville, FL	Controlled clinical/efficacy/field safety/acceptability
12781	Dr. S. T. Currin	Mayfair Animal Hospital Cary, NC	Controlled clinical/efficacy/field safety/acceptability
12782	Dr. A. Ellis	River Cove Animal Hospital Williston, VT	Controlled clinical/efficacy/field safety/acceptability
12829	Dr. J. Hugenbois	Beattie Animal Hospital Brantford, Ontario, Canada	Controlled clinical/efficacy/field safety/acceptability
12906	Dr. D. Weiner	Dogwood Hospital for Animals Atlanta, GA	Controlled clinical/efficacy/field safety/acceptability
12907	Dr. R. Lange Dr. R. Lange	Lange Animal Hospital Knoxville, TN	Controlled clinical/efficacy/field safety/acceptability
13713	Dr. R. L. Sifferman	Grant Avenue Pet Hospital Springfield, MO	Controlled clinical/acceptability
12666	Dr. M. Gilman	Hazelton-LRE Kalamazoo, MI	Reproductive safety
12932	Dr. M. Gilman	Hazelton-LRE Kalamazoo, MI	Pup safety
12663	Dr. A. D'ver	White Eagle Labs Doylestown, PA	Repeated treatment tolerance (Corroborative)

TABLE 2: EFFICACY OF PYRANTEL (5 MG/KG) IN HEARTGARD-30® PLUS FORMULATION AGAINST NATURAL AND/OR INDUCED INFECTIONS OF INTESTINAL TRACT NEMATODES

Parasite	**Number of Dogs Treated**	**% Efficacy Compared to Control**	**Trial #**	**Treatment**
Toxocara canis	6	97.5	12444	Pyrantel*
Toxocara canis	6	91.9	12489	Pyrantel
Toxocara canis	8	88.3	12591	Iver/pyrantel**
Toxocara canis	8	80.1	12591	Pyrantel
Toxascaris leonina	8	100.0	12592	Iver/pyrantel
Toxascaris leonina	8	95.9	12592	Pyrantel
Toxascaris leonina	7	92.0	12665	Pyrantel
Ancylostoma caninum	8	100.0	12592	Iver/pyrantel
Ancylostoma caninum	8	>99.0	13095	Iver/pyrantel
Ancylostoma caninum	7	>99.0	12665	Pyrantel
Ancylostoma caninum	8	96.8	12592	Pyrantel
Ancylostoma caninum	6	92.8	12444	Pyrantel
Ancylostoma caninum	8	89.9	12591	Pyrantel
Ancylostoma caninum	8	86.3	12591	Iver/pyrantel
Uncinaria stenocephala	8	>99.0	12592	Iver/pyrantel
Uncinaria stenocephala	8	>99.0	13095	Iver/pyrantel
Uncinaria stenocephala	8	96.3	12592	Pyrantel
Uncinaria stenocephala	7	93.4	12665	Pyrantel

* pyrantel pamoate at 5 mg/kg in the HEARTGARD-30® Plus vehicle
** pyrantel pamoate at 5 mg/kg with 6 mcg/kg in the HEARTGARD-30® Plus formulation intended for market

TABLE 3: SUMMARY OF FIELD TRIALS WITH HEARTGARD-30 Plus

Trial	Female	Male	Total	# Owners	Age	Weight	HG-30/N*	HG-30+**	Site	Investigator
12774	11	20	64	45	6 ms-13 y	4-68 kg	16	48	Carterville, Il.	R. S. Blakely
12779	34	17	51	29	9 ms-13 y	2.7-68 kg	13	38	Winter Park, Fl.	K. E. Acre
12780	33	19	52	30	6 ms-14 y	2.6-46 kg	13	39	Gainesville, Fl.	M. W. Coleman
12781	37	15	52	32	1 - 13 y	1.6-54 kg	13	39	Cary, N.C.	S. T. Currin
12782	37	15	52	39	6 ms-14 y	6.4-49 kg	13	39	Williston, Vt.	A. J. Ellis
12829	29	27	56	37	1 - 12 y	2.4-39 kg	14	42	Brantford, Ontario, Canada	J.W. Hugenbois
12906	36	16	52	35	1 - 13 y	4.1-47 kg	13	39	Atlanta, Georgia	D. Weiner
12907	30	21	51	28	7 ms-12 y	4.0-43 kg	12	39	Knoxville, Tn	R. L. Lange
Total	280	150	430	275	-	-	107	323	-	-

*HEARTGARD-30 tablets and NEMEX/Pfiser Inc. US or HEARTGARD-30 tablets and PYR-A-PAM 2/Rotar FIB London Trial #12829 was the only one in which PYR-A-PAM 2 was used
**HEARTGARD-30 Plus

VI. ATTACHMENTS

Veterinarian's insert
Package insert
5 to 25 lb body weight (shipping carton, outer and inner drug cartons)
26 to 50 lb body weight (shipping carton, outer and inner drug cartons)
51 to 100 lb body weight (shipping carton, outer and inner drug cartons)

Copies of these 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.