I. GENERAL INFORMATION

A. File Number

NADA 138-412

B. Sponsor

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

C. Proprietary Name

HEARTGARD^{30}®

D. Established Name

Ivermectin tablets

E. Dosage Form

Physical Description of the product

F. Amount of Active Ingredient

X mg/ml, g/lb, etc.

G. How Supplied

Size and Description of container

H. Dispensing Status

For use by or on the order of a licensed veterinarian.

I. Dosage Form, Route of Administration and Recommended Dosage

The ingredients in HEARTGARD^{30} are formulated into various sized tablets to be administered orally (swallow) as appropriate for the weight of the dogs (see below) at monthly dosing intervals.

The tablets supply the recommended minimum dose level of 6.0 mcg ivermectin per kilogram (2.72 mcg/lb) of body weight.

Dog Weight	Tablets Per Month	Ivermectin Per Tablet	Product Number
Up to 25 lb	1	68 mcg	38171
26 to 50 lb	1	136 mcg	38172
51 to 100 lb	1	272 mcg	38173

Give dogs over 100 lb the appropriate combination of these tablets.

J. Indication

For use in dogs to prevent canine heartworm disease. HEARTGARD[30] (ivermectin) eliminates the tissue stage of heartworm larvae (*Dirofilaria immitis*).

II. EFFECTIVENESS

Pivotal Studies

The New Animal Drug Application for ivermectin tablets contains adequate and well controlled studies which demonstrate their efficacy in preventing heartworm infections in dogs.

Dose Titration and Confirmation

The effectiveness of ivermectin tablets was established in 11 controlled (necropsy) trials. These trials which included 370 ivermectin-treated dogs and 83 unmedicated control dogs were utilized to select and confirm the appropriate dose. The chewable tablet formulation used in the first three trials (see Table 1) was later found unacceptable. The active ingredient of the chewable tablet, ivermectin, was the same as that of the market formulation. The chewable tablets performed similarly in the early trials to the market formulation tablet used in the more recent eight efficacy trials (and all of the field trials).

The methods used in the induced infection studies were those described by McCall (J. Georgia Entomol. Soc. (16) 1st Supplement 283-293, 1981).

At necropsy in each trial, the pleural cavity, pre-cava, right atrium, right ventricle and pulmonary arteries and branches in the lungs were examined for worms. The worms (*D. immitis*) from each dog were counted, sexed and preserved in fixative.

Total numbers of heatworms found at necropsy were analyzed in each trial. The data were transformed for calculation of geometric means and percent efficacies to the natural logarithm of (count +1).

Percent efficacy was calculated using the formula:

$$\text{Percent Efficacy} = \frac{\text{Geometric Mean of Heartworm Counts for Controls} - \text{Geometric Mean of Heartworm Counts for the Ivermectin Treatment Group}}{\text{Geometric Mean of Heartworm Counts for Controls}} \times 100$$

The trials are identified in table 1 and the results are summarized in tables 2 and 3.

The recommended minimum dose of 6 mcg of ivermectin per kilogram of body weight was selected although a lower dose (3.3 mcg/kg) may be as effective. In addition to the results of the dose titration and confirmation trials, factors concerning the practicality of incorporating minute amounts of drug in a reasonably sized tablet with good drug uniformity and the practical use of the product were considered. The target

dose of 6 mcg per kilogram of bodyweight was selected from titration study 10855 as the lowest dose providing 100% protection when the dosing interval was extended to 60 days to simulate a missed-dose circumstance. Extended interval dosing trials are summarized in table 3. The selected dose has a very wide margin of safety.

Controlled Clinical (Field) Trials

The acceptability of the market formulation was tested in seven similar controlled clinical or field trials. The trials are further identified in table 1 and table 4. At initiation of the trials seven hundred one dogs received treatment with ivermectin oral tablets and 194 dogs served as controls receiving daily diethylcarbamazine (DEC). The dogs were generally randomly allocated to treatment based on order of presentation. In four of the studies, in addition to daily DEC the controls received a monthly placebo tablet.

The dogs in each trial were tested for patent heartworm infections using a modified Knott technique or filtration/concentration method at the beginning and at strategic points during the trials, most frequently at 4 to 5 months, 7 to 9 months, and some at about 12 months. All of the dog owners were voluntary participants administering the treatments, making observations, keeping records and having periodic contact with the investigator to monitor their activities and examine the dogs. The dogs were housed and maintained in the customary manner of the owners' household or kennel.

Ivermectin was administered monthly in different sizes of swallow tablets based on the weight of the dog. The tablets were designed to provide a minimum monthly dose of 6 mcg/kg of body weight in four trials and 2 mcg/kg of body weight in three trials. The actual doses administered ranged from approximately 1.5 to 53 mcg/kg. The highest dose was achieved with the 68 mcg tablet given to an eight-week old yorkshire terrier which weighed 2.8 lb. Approximately 95% of the ivermectin-treated dogs in these trials received less than 15 mcg/kg.

Individual dogs received up to over one year of treatment. Over 70 different breeds or types of dogs (including collies) under a wide variety of circumstances participated in the trials. Puppies as young as 8 weeks old were included in the trials. As expected during trials lasting up to over one year, many dogs were exposed to a wide variety of veterinary or animal health products including vaccines, anesthetics, analgesics, anthelmintics, ectoparasiticides (including flea control products), antimicrobials, antibiotics, anti-inflammatories, steroids, hormones and a variety of ophthalmic and dermatologic preparations.

The most frequent clinical or adverse observations were vomiting, loose feces or diarrhea, decreased activity and decreased appetite. They were observed at similar incidences in both the DEC-treated controls and the ivermectin-treated dogs. None of these observations was thought to be due to treatment.

One dog experienced an apparent allergic reaction within three hours after ivermectin treatment on two occasions. The dog recovered without apparent residual effects.

There were no other clinically significant observations which were related to treatment.

Three hundred forty-eight of the ivermectin-treated dogs and 96 of the DEC (control) dogs were evaluated for efficacy after 7 months to l year of treatment with 197 of the ivermectin-treated dogs and 48 of the DEC controls being retested at one year to 16 months. The remainder of the dogs starting on trial were withdrawn by their owners for a wide-variety of reasons most of which were unrelated to treatment. Three animals were withdrawn from the trials, one for vomition, one for inappetence and one with apparent allergic reaction. The most common reasons for declining numbers of patients was the owner moving from the area, change of ownership of an animal, or death due to unrelated causes.

Only two dogs which had been identified as not being infected before the start of the trials had circulating microfilariae at the end of the trials. One of these dogs was a DEC-treated control. The owner of the other dog, one treated with ivermectin, admitted that he had failed to administer the tablets on several occasions.

Conclusions

Three hundred seventy dogs in controlled efficacy trials were treated with ivermectin. Of the 83 dogs treated at monthly intervals in natural infection trials, or treated 30 days after induced infection, with doses of ivermectin at 3.0 mcg/kg or greater, only 2 dogs developed infections. Even when the treatment interval was extended to 45 or 60 days following infection, only 2 of 88 dogs given ivermectin at 6.0 mcg/kg or more developed infections.

Therefore, HEARTGARD$^{30®}$ with a monthly dose of 6.0 mcg/kg is effective in preventing canine heartworm disease.

III. TARGET ANIMAL SAFETY

Pivotal Studies

Five toxicity or tolerance trials, three breeding animal safety trials and three trials on the acceptability of treating dogs with patent heartworm infections (heartworm positive dogs), have been conducted. The trials are further identified in table 1.

Because high levels of ivermectin are required for appropriate safety testing compared to the low dose and dilute nature of the oral tablet market formulation, the market formulation could not be used to administer the necessary elevated levels in these trials. Impractical and irrelevant numbers of tablets would have been required, therefore, other formulations were utilized (as described below). When lower doses were administered the heartworm-positive-dog studies, the market formulation was used. The ivermectin used in all of these studies is the same as the ivermectin in the market formulation.

Toxicity and Tolerance

TT#78-038-0 - Tolerance - Fourteen Week Toxicity Study in Dogs
Twenty male and 20 female beagles from 39 to 43 weeks of age were divided into five treatment groups of eight dogs each, four of each sex, and were allocated to treatment. Treatments were administered daily for 94 to 95 consecutive days by intubation. Three groups received ivermectin at 500, 1,000 or 2,000 mcg/kg/day and

two groups served as controls receiving either sesame vehicle or deionized water, also daily.

The dogs were evaluated based on weights, ophthalmologic examinations, electrocardiograms, hematologic and serum biochemical studies, urinalyses and appropriate gross and histopathologic examinations.

No potentially drug-related abnormalities were detected in any examination or sample, and no adverse reactions were observed in any dog receiving ivermectin at 500 mcg/kg/day during the 14 week study.

Mydriasis was detected in dogs receiving 1000 mcg/kg/day after 15 days. A retardation in weight gain was also observed in this treatment group. No other treatment-related effects were detected during examinations or in samples from the group.

No abnormalities or adverse reactions were detected in dogs after the first dose of 2,000 mcg/kg. Mydriasis was first clinical sign observed and was eventually seen in all dogs in this group, and more severe signs were seen in some dogs including salivation, tremors, ataxia, anorexia, dehydration and weight loss. No other treatment-related changes were found.

TT#79-2869 - Acute Toxicity in Dogs
Two male and two female beagle dogs, 10 to 14 months of age, were allocated to each of four treatment groups: ivermectin at 2,500 5,000 or 10,000 mcg/kg body weight or vehicle. Sesame oil was the drug solvent or vehicle. The treatments were administered by gastric intubation. The dogs were observed for 14 days.

Emesis, salivation, mydriasis, absence of pupillary response and tremors were seen in some dogs following treatment at the two higher dose levels. One of the dogs given the highest dose became ataxic and sedated. The dog recovered from the sedation within 48 hours of treatment and from the remaining signs 72 hours after treatment. Mydriasis and absence of pupillary response were the only clinically significant signs seen at the lowest ivermectin dose level (2,500 mcg/kg). None of the signs persisted past the sixth day after treatment.

TT#81-2500 - Acute Toxicity in Dogs
Each of 2 male and 2 female beagle dogs, 6 to 9 months of age, were allocated to receive ivermectin at 5,000, 10,000, 20,000, 40,000 or 80,000 mcg/kg body weight or sesame oil vehicle. The treatments were administered by gastric intubation. The dogs were observed for 14 days.

Emesis following treatment was seen in at least one dog in all treatment groups (including vehicle) except 40,000 mcg/kg. Mydriasis was seen in most dogs at all ivermectin dose levels. Ataxia and tremors were seen at doses of 10,000 mcg/kg and greater. Salivation was noted in some dogs at the two highest ivermectin dose levels. One dog given 40,000 mcg/kg and three dogs given 80,000 mcg/kg were unable to stand beginning four to six hours after treatment. One of these dogs (at the highest dose level) was up the next morning; however, the other three remained down, became comatose and died. Three of four dogs given 40,000 mcg/kg and two of four dogs given 80,000 mcg/kg survived. All of the surviving ivermectin-treated dogs appeared normal at the end of the study.

TT#81-025-0 - Acute Toxicity in Young Dogs
Five groups of three male and three female pups (11 to 12 weeks old) were allocated to receive subcutaneous injections of ivermectin in a micelle solution at 4,700, 9,400, 18,800, 37,500 or 75,000 mcg/kg body weight while a sixth group of two female and three male pups received only vehicle.

The 15 day trial included observations for clinical signs and an ophthalmologic examination of survivors eight days after treatment. All dogs were necropsied.

Mydriasis, negative pupillary response to light and ataxia were detected the day after treatment in dogs receiving 4,700 mcg/kg. All dogs in this group appeared normal by the seventh day after treatment.

Emesis was seen in one dog given 9,400 mcg/kg and in one dog given 75,000 mcg/kg. Mydriasis, ataxia, salivation, negative pupillary light response, decreased activity, tremors and death were experienced in groups receiving ivermectin at 9,400 mcg/kg and greater doses.

No treatment-related abnormalities were detected in the ophthalmic examination of surviving dogs eight days after treatment.

Other than agonal changes no treatment-related histologic changes were detected.

ASR 11017 - Acute Toxicity in Collies (Breed)
Sixteen purebred collies, eight of each sex and half of the animals affected with collie eye anomaly (CEA) and half free of the anomaly, were utilized to determine if ivermectin was toxic in collies at levels not generally toxic to other breeds and if collie eye anomaly (CEA) was related to sensitivity.

The dogs were allocated to four treatment groups so that each sex with each eye status was represented in each treatment group. The four treatment groups were: untreated control, ivermectin at 50 mcg/kg, 200 mcg/kg or 600 mcg/kg. Ivemectin was administered orally in a fractionated coconut oil solution.

Frequent clinical neurologic examinations were made for 7 days. Necropsies and histopathologic evaluations and tissue ivermectin assays were made on three dogs, two of which where showing severe signs of toxicity and one control. In a second phase, the three remaining dogs, which had originally served as controls, were given ivermectin at 50 mcg/kg and examined for 4 days.

Signs of toxicity were detected in a female free of CEA after receiving ivermectin at 600 mcg/kg and in a CEA-affected male after receiving 200 mcg/kg. The evolving signs included ataxia with gradually increasing hypermetria, depression, tremors, paresis, recumbency, mydriasis, drooling, paralysis and coma with predominantly diaphragmatic respiration. The affected dog in the highest dose group was euthanized in extremis approximately 28 hours after treatment, and the other affected dog died approximately 5l hours after treatment.

The histologic findings, including pulmonary congestion, pulmonary edema and multifocal hemorrhages in central nervous tissue were all likely related to agonal death or the euthanasia technique and were not felt to be effects of ivermectin treatment.

Ivermectin tissue assays showed high concentrations of ivermectin in the central nervous system.

Two other dogs, one male in the 600 mcg/kg group and one female in the 200 mcg/kg group, both not affected with CEA, showed slight transitory signs.

The signs seen in the affected collies were similar to those seen in the dogs in the toxicity and tolerance studies at doses of 2500 mcg/kg and greater.

Sensitivity to ivermectin did not appear to be related to CEA. None of the collies given ivermectin at 50 mcg/kg showed signs of toxicity.

Breeding Animal Safety

Teratology in Laboratory Animals

Ivermectin has been shown to be teratogenic in rats, rabbits, and mice at or near maternotoxic dose levels. At these high doses, evidence of a teratogenic effect is limited to cleft palate that occurs at a low frequency in all three species and clubbing of the forepaws which occurs only in rabbit fetuses. Mice are the most sensitive species to the effects of Ivermectin with maternotoxlclty at a dose of 200 mcg/kg/day and teratogenicity at 400 mcg/kg/day. In rabbits 6000 mcg/kg/day was maternotoxic and teratogenlc, and teratogenicity was also evident at a dose of 3000 mcg/kg/day. The threshold for both maternotoxicity and teratogenicity in rats was 10,000 mcg/kg/day.

TT#80-704-0 - Teratology in Dogs
A solution of ivermectin in sesame oil was administered by stomach tube at a dose level of 500 mcg/kg to one group of 14 pregnant beagles on Days 5, 15, 25 and 35 of gestation, and a second group of 15 pregnant beagles received the same dosage of ivermectin on Days 10, 20, 30 and 40 of gestation. An additional group of 12 pregnant beagles served as controls and received the vehicle on Days 5, 10, 15, 20, 25, 30, 35, and 40 of gestation. All dogs were hysterectomized on Day 48 of gestation and the uterine contents removed and examined. All fetuses were weighed and examined for external, visceral, and skeletal alterations.

The pregnant females were observed at]east once daily for clinical signs of toxicity and were weighed frequently during the trial.

There were no clinical signs of toxicity among pregnant female dogs receiving ivermectin. Average maternal body weight gains were not affected by ivermectin treatment.

Ivermectin had no effect on the reproductive status of pregnant bitches as monitored by the number of implants, resporptions, and live and dead fetuses per pregnant female.

There was no evidence of a teratogenic effect at external, visceral, or skeletal examination of fetuses from bitches treated with ivermectin. At initial examination, there was an apparent increase in sternebral variations in fetuses from ivermectin-treated bitches. The evaluation of these variations is highly subjective and a

reexamination of the fetuses in this study by additional pathologists, not advised of the treatment groups, found no meaningful differences in the incidences of litters with these variations between treated and untreated control groups. The sternebral ossification process and the size, shape and orientation of sternebra are highly variable. The type of variations seen in this study have been reported to occur at high and variable frequencies in fetuses from untreated bitches in the colony used in this study and in other colonies. These variations are not detectable after birth.

ASR 11014 - Safety in Breeding and Pregnant Bitches
Thirty non-pregnant beagle bitches of proven reproductive performance were randomly allocated to two treatment groups with the first ten animals in each group to come into estrus used to complete the trial. The two treatments were vehicle or ivermectin at 600 mcg/kg in fractionated coconut oil; both were administered orally. The bitches were treated monthly (at least twice) until coming into estrus and being bred. Treatments were then administered on approximately days 10, 25 and 45 of gestation (from first acceptance of the stud) and continued on a monthly regimen until the pups were weaned at six weeks of age. Therefore, each bitch that became pregnant received at least five or as many as ll treatments depending on when she came into estrus.

All of the bitches were given physical examinations including evaluations of hematology and serum chemistry and urinalysis prior to the first treatment and at the end of the study. The animals were frequently observed throughout the trial.

Pups were closely examined at whelping and at weaning. All dead pups including any stillborns were necropsied.

No meaningful differences were detected between groups for incidence or frequency of any clinical observations.

All bitches in the ivermectin group were successfully bred, while nine of the 10 vehicle-treated bitches became pregnant.

An average of 6 live pups was born to each pregnant ivermectin-treated bitch, with 93.3% of the pups whelped surviving to weaning. In the vehicle-treated group, each pregnant bitch whelped an average of 5.44 pups with 85.7% of the pups whelped surviving to weaning.

No anomalies were found in the bitches in either physical examination. Laboratory studies detected some values outside of reference 'normal' parameters in both treatment groups; however, no patterns were evident and the variations were not attributed to treatment. No clinically meaningful differences were observed between groups for bitch or puppy weights.

Congenital abnormalities were detected in four puppies from bitches in the vehicle group and two puppies from the ivermectin group.

No bitches died during the trial. Seven puppies from the vehicle group and four puppies from the ivermectin group died between birth and weaning.

None of the observations was related to ivermectin treatment, as they occurred at similar or greater incidence in the control group.

From this trial, it is obvious that ivermectin, even at high and repeated doses, has no effects on the breeding or reproductive performance of canine females.

ASR 11015 - Safety in the Breeding Male (Stud) Dog
Twelve healthy male beagle dogs of proven breeding performance were divided into six replicates of two dogs each in order of pretreatment average sperm count ranking. Within each replicate, the dogs were randomly allocated to receive either tap water (controls) or ivermectin at 600 mcg/kg in a fractionated coconut oil solution. Treatments were administered at 30-day intervals from the start of the trial to necropsy so that each stud received 8 treatments.

Semen samples were collected from each stud every third day beginning 28 days prior to the first treatment and continuing for 83 days after that treatment. Standardized techniques were used in the collection and in the evaluation of the semen samples. Beginning approximately two weeks after the last sample was collected, each stud was bred to two bitches. The studs were necropsied after the last of the bitches whelped.

The studs were given a physical examination prior to the first treatment and at the end of the trial. Hematology, blood and serum chemistry and urinalyses were performed prior to the first treatment and at the end of the study. The studs were closely observed throughout the trial. The studs were weighed prior to each treatment and at the end of the trial. The necropsy evaluation included the gross examination of the organ systems as well as the histopathological examination of the testes and epididymides.

The results of each stud being bred to two healthy untreated bitches were evaluated for breeding behavior, fertility (conception rate), litter size, puppy body weights and puppy abnormalities. Any puppies that died or were born dead were closely examined or necropsied.

There were no meaningful differences between treatment groups in incidence and frequency of significant clinical observations or in stud weight changes.

No anomalies were detected by the physical examinations of the studs before or after treatment. While certain clinical chemistry and urinalysis values for individual dogs in both the control and ivermectin treatment groups may be considered to be outside expected normal values, these variations were scattered randomly, occurring without apparent patterns. The variations were not indicative of any clinical syndrome, were seen in both groups before treatment as well as at the end of the trial and are not attributable to treatment.

No pattern of differences were found between ivermectin-treated dogs and controls for total sperm counts, percent progressively motile sperm or speed of progression of sperm. No deviations from normal were experienced for semen color or pH, or for sperm morphology or abnormalities (primary, secondary or tertiary).

One bitch bred to an ivermectin-treated stud did not become pregnant. The first bitch bred to that stud did become pregnant. All other breedings in both treatment groups were successful. The fertility index (number conceived per number mated x 100) for the ivermectin group was 91.7 and 100 for the controls. The mean fertility rate at the

colony is 90.2%. Considering the prolonged period of manual semen collection, no unexpected or breeding behavior was experienced in the studs.

No abortions were observed in bitches bred to studs of either group.

No meaningful differences were observed between groups for litter size or for average puppy weight in a litter. The only observed important abnormalities were in puppies from the control group breeding and included one undershot jaw, and one cleft palate.

At necropsy, no differences were observed histologically in the testes and epididymides between the ivermectin-treated and water-placebo-treated-control groups. The testes and epididymides of both groups were essentially normal. Spermatogenesis occurred in an organized manner in both groups. No treatment related pathologic lesions were found in any of the dogs.

This trial demonstrates that repeated administration of ivermectin at doses many times greater than the dose for heartworm prevention has no clinically significant effect on dogs and specifically demonstrates that ivermectin is safe for use in breeding male (stud) dogs.

ASR 10843, 10844 and 10972 - Acceptability in Dogs With Patent Heartworm Infections (Microfilariae-positive Doqs)
The effects of ivermectin treatment on dogs with patent heartworm infections as indicated by the presence of circulating microfilariae was examined in three similar studies (see table l for identification of trials).

In these trials, a total of 80 dogs with naturally acquired *Dirofilaria immitis* infections confirmed using a modified Knott technique, were utilized. The animaIs were mature dogs of both sexes and several different breeds and crosses.

In each trial, the dogs were randomly allocated to the four treatment groups; untreated control, ivermectin at 2 or 10 mcg/kg in the swallow tablet formulation or at 400 mcg/kg in a fractionated coconut oil solution. Each of the ivermectin treatments was administered orally three times at monthly intervals (28-30 days). The dogs were closely observed throughout the trial. Blood samples were taken prior to the first treatment and several times during the trial and evaluated using a modified Knott technique or direct count method. Patent infections were assumed to continue as no adulticidal agent was administered. Observations and sampling continued until the end of the trials, approximately two weeks after the third treatment. The dogs were given a physical examination prior to the initial treatment and at the end of the trials.

Adverse reactions, possibly related to the destruction of microfilariae and release of antigen following the oral administration of ivermectin to heartworm-positive dogs included varying levels of vomiting, soft, poorly-formed feces and diarrhea (some with blood flecks or a bloody tinge). In ASR 10843, most of these reactions were seen after the third treatment. More reactions were observed in the dogs given ivermectin at 400 mcg/kg than in those given 2 or l0 mcg/kg.

The types of reactions seen in these trials are commonly observed in dogs, were transitory and did not appear to endanger the dogs' health. None of the dogs

experienced the severe DEC-type shock reaction. These results agree with the finding of Boreham (Boreham, P.F.L. and Atwell, R.B.: Absence of shock-like reactions to ivermectin in dogs infected with *Dirofilaria immitis*. Journal of Helminthology: 57, 279-281,1983).

Conclusions

With a dose of 6 mcg/kg being effective against the tissue 30 larval stage of *Dirofilaria immitis*, HEARTGARD (ivermectin oral tablet) has a wide margin of safety in normal dogs. When administered daily to beagles for 14 weeks, ivermectin at 500 mcg/kg had no adverse effects and 1,000 mcg/kg had only mild effects. No adverse effects were detected after a single dose of 2,000 mcg/kg. In acute toxicity studies, deaths did not occur at oral doses below 40,000 mcg/kg. When toxic levels of ivermectin are administered to dogs, the signs seen may include mydriasis, loss of pupillary response, loss of menace reflex, depression, ataxia, tremors, recumbency, salivation, coma and death.

Even in those individual dogs, particularly of the collie breed, that have an unusual and extreme sensitivity to the toxic effects of ivermectin, an adequate safety margin exists with HEARTGARD^{30}.

For dogs with patent heartworm infections, treatment with HEARTGARD^{30} poses no threat to their health.

Neither the reproductive performance nor the offspring of breeding females or males were adversely affected by repeated, relatively high (500-600 mcg/kg) doses of ivermectin.

Table 1: Identification of investigators and trial location for ivermectin effectiveness and animal safety trials.

Trial Number	Formulation*	Investiqator(s)	Location/ Address	Objective or Type of Trial
ASP 8397	C	Dr. John W. McCall	University of GA, Athens, GA	Efficacy - Dose Titration and Confirmation
ASP 8397	C	Dr. Lari Cowgill	Brunswick, GA	Efficacy - Dose Titration and Confirmation
ASP 8400	C	Dr. John W. McCall	University of GA, Athens, GA	Efficacy - Dose Titration and Confirmation
ASP 8762	C	Dr. Kenneth Acre	Howell Branch Animal Hospital, Winter Park, FL	Efficacy - Dose Titration and Confirmation
ASP 9730	M	Dr. Kenneth Acre	Howell Branch Ani. Hospital, Winter Park, FL	Efficacy - Dose Titration and Confirmation

Trial Number	Formulation*	Investiqator(s)	Location/ Address	Objective or Type of Trial
ASP 9731	M	Dr. John W. McCall	University of GA, Athens, GA	Efficacy - Dose Titration and Confirmation
ASP 10585	M	Dr. John W. McCall	University of GA, Athens, GA	Efficacy - Dose Titration and Confirmation
ASR 10733	M	Dr. Kenneth Todd	University of IL Urbana, IL	Efficacy - Dose Titration and Confirmation
ASP 10847	M	Ms. Lyndia Blair	Merck & Co., Inc. Rahway, NJ	Efficacy - Dose Titration and Confirmation
ASP 10847	M	Dr. John W. McCall	University of GA, Athens, GA	Efficacy – Dose Titration and Confirmation
ASR 10854	M	Dr. John W. McCall	University of GA, Athens, GA	Efficacy - Dose Titration and Confirmation
ASR 11244	M	Dr. Kenneth Todd	University of IL Urbana, IL	Efficacy- Dose Titration and Confirmation
ASR 10855	M	Dr. John W. McCall	University of GA, Athens, GA	Efficacy - Dose Titration and Confirmation
ASR 10641	M	Dr. G. C. Troy Dr. T. M. Craig	Texas A&M Univ. College Station, TX	Practical Safety and Efficacy Field Trial
ASR 10837	M	Dr. Kenneth Acre	Howell Branch Ani. Hospital, Winter Park, FL	Practical Safety and Efficacy Field Trial
ASR 10943	M	Dr. Mark J. Kopit Dr. James N. Ross	Angell Memorial Hospital, Tufts Univ., Jamaica Plains, MA	Practical Safety and Efficacy Field Trial
ASR 10660	M	Dr. M.W. Coleman	Suburban Animal Hosp. Gainesville, FL	Practical Safety and Efficacy Field Trial
ASR 10861	M	Dr. William Jackson	Ani. Med. Clin. Inc. Lakeland, FL	Practical Safety Field Trial

Trial Number	Formulation*	Investiqator(s)	Location/ Address	Objective or Type of Trial
ASR 10862	M	Dr. Kenneth Acre	Howell Branch Animal Hospital, Winter Park, FL	Practical Safety Field Trial
ASR 11093	M	Dr. Ben Johnson	Westbury Animal Hospital, Houston, TX	Practical Safety Field Trial
TTT78-038-0	S	Dr. Charles Tate	MSDRL, Merck & Co., Inc., West Point, PA	Chronic Toxicity – Tolerance
TT79-2869	S	Dr. Jerome Mandel	MSDRL, Merck & Co., Inc., West Point, PA	Acute Toxicity
TT81-2500	S	Dr. James MacDonald	MSDRL, Merck & Co., Inc., West Point, PA	Acute Toxicity
TT81-025-0	I	Dr. Jerome Mandel	MSDRL, Merck & Co., Inc., West Point, PA	Acute Toxicity in young dogs
ASR 11017	S	Dr. Robert Henry	Buckshire Corp., Perkasie, PA	
ASR 11017	S	Dr. Sheldon Steinberg	Univ. of PA, PhiladeIphia, PA	Acute Toxicity in collies
TT8O-704-0	S	Dr. R. T. Robertson	MSDRL, Merck & Co., Inc., West Point, PA	Teratology
ASR 11014	S	Dr. Martin R. Gilman	LRE, Inc., Kalamazoo, MI	Safety in breeding and pregnant bitches
ASR 11015	S	Dr. Martin R. Gilman	LRE. Inc., Kalamazoo, MI	Safety in the breeding male dog
ASR 10843	M,S	Dr. John W. McCall	University of GA, Athens, GA	Acceptability in microfilariae positive dogs
ASR 10844	M,S	Dr. Byron L. Blagburn	Auburn University, Auburn, AL	Acceptability in microfilariae positive dogs
ASP 10972	M,S	Dr. J. C. Schlotthauer Bert E. Stromberg	University of MN, St. Paul, MN	Acceptability in microfilariae positive dogs

M = Oral tablet - market formulation
S = Solutions administered by Oral intubation or orally
I = Solution administered by subcutaneous injection

Table 2. Summary of Trial Results; The efficacy of various doses of ivermectin administered orally, in preventing the development of adult *D. immitis* in dogs for each trial.

ASR 8397
(Chewable Tablet)
(Natural Infections; from 15-16 months exposure)

Treatment* Ivermectin mcg/kg	Number of Dogs/Treatment	Number of Dogs With Adult Worms Found	Range of Worm Counts In Infected Dogs	Total Worms Found	Geometric Mean** of Worm Counts	Percent Efficacy
Vehicle control	8	5	1-11	30	2.04	--
0.33	8	5	1-11	24	1.63	20
1.0	8	0	0	0	0	100
3.3	8	0	0	0	0	100
10.0	8	0	0	0	0	100
33.0	8	0	0	0	0	100

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

ASR 8400
(Chewable Tablet)
(Natural Infections; from 19 months exposure)

Treatment* Ivermectin mcg/kg	Number of Dogs/Treatment	Number of Dogs With Adult Worms Found	Range of Worm Counts In Infected Dogs	Total Worms Found	Geometric Mean** of Worm Counts	Percent Efficacy
Vehicle control	8	5	1-12	32	2.08	--
0.33	8	4	1-3	7	0.62	70
1.0	8	0	0	0	0	100
3.3	8	0	0	0	0	100
10.0	8	0	0	0	0	100
33.0	8	0	0	0	0	100

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

ASR 8762
(Chewable Tablet)
(Natural Infections; from 18 months exposure)

Treatment* Ivermectin mcg/kg	**Number of Dogs/Treatment**	**Number of Dogs With Adult Worms Found**	**Range of Worm Counts In Infected Dogs**	**Total Worms Found**	**Geometric Mean** of Worm Counts**	**Percent Efficacy**
Vehicle control	8	4	1-3	7	0.62	--
0.33	8	1	1	1	0.09	85
1.0	8	0	0	0	0	100
3.3	7	0	0	0	0	100
10.0	8	0	0	0	0	100
33.0	7	0	0	0	0	100

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

ASR 9730
(Market Formulation)
(Natural Infections; from 10 months exposure)

Treatment* Ivermectin mcg/kg	**Number of Dogs/Treatment**	**Number of Dogs With Adult Worms Found**	**Range of Worm Counts In Infected Dogs**	**Total Worms Found**	**Geometric Mean** of Worm Counts**	**Percent Efficacy**
Vehicle control	8	7	5-26	70	6.3	--
0.3	8	6	1-7	29	2.5	60.1
1.0	8	6	1-7	29	2.5	60.1
1.0	8	1	1	1	0.1	98.3
3.3	8	0	0	0	0	100
Bimonthly	8	7	1-9	37	3.6	43.4

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

ASR 9731
(Market Formulation)
(Natural Infections; from 9 months exposure)

Treatment* Ivermectin mcg/kg	**Number of Dogs/Treatment**	**Number of Dogs With Adult Worms Found**	**Range of Worm Counts In Infected Dogs**	**Total Worms Found**	**Geometric Mean** of Worm Counts**	**Percent Efficacy**
Vehicle control	8	8	5-25	98	10.58	--
0.3	8	7	1-8	32	3.11	70.6
1.0	8	0	0	0	0	100
3.3	8	0	0	0	0	100
Bimonthly	8	6	1-8	21	1.77	83.3

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

ASR 10585
(Market Formulation)
(Inducted Infections; with ~50 larvae/dog)

Treatment* Ivermectin mcg/kg	**Number of Dogs/Treatment**	**Number of Dogs With Adult Worms Found**	**Range of Worm Counts In Infected Dogs**	**Total Worms Found**	**Geometric Mean** of Worm Counts**	**Percent Efficacy**
Vehicle control			14-30	157	21.8	--
0.3			11-29	124	12.4	43.1
1.0			1-27	55	5.1	76.7
2.0			0	0	0	100
3.3			0	0	0	100
2.0 45 days after infection			3-5	13	1.0	95.3

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

ASR 10733
(Market Formulation)
(Induced Infections; with ~50 larvae/dog)

Treatment* Ivermectin mcg/kg	**Number of Dogs/Treatment**	**Number of Dogs With Adult Worms Found**	**Range of Worm Counts In Infected Dogs**	**Total Worms Found**	**Geometric Mean** of Worm Counts**	**Percent Efficacy**
Vehicle control	7	7	19-38	199	27.72	--
0.3	7	7	25-36	203	28.79	0
1.0	7	6	9-31	136	12.98	53.2
2.0	7	2	2 & 18	20	0.70	97.2
3.3	7	2	1 & 9	10	0.53	98.1
2.0 45 days after infection	7	6	6-32	110	10.04	63.8

* Monthly in natural infection trials or 30 days after induced infections unless otherwise indicated.
** Based on transformation to the natural logarithm of (count +1).

Table 3: Summary of Trial Results; The efficacy of various doses of ivermectin administered orally, in preventing the development of adult *D. immitis* in dogs for each trial.

ARS 10847
(Induced Infections; with ~30 larvae/dog)

Treatment Ivermectin mcg/kg	**# Dogs/Treatment**	**Treatment Days PI**	**Necropsy Mos PI**	**Number of Dogs With Adult Worms Found**	**# Worms Range**	**Percent Efficacy**
Vehicle control	7	29	5 (2 dogs)	2	22, 23	--
Vehicle control	7	29	12-1/2 (5 dogs)	5	13-25	--
3.0	7	29	5 (2 dogs)	0	--	100
3.0	7	29	12-1/2 (5 dogs)	0	--	100

PI = post infection

ARS 10847
(Induced Infections; with ~50 larvae/dog)

Treatment Ivermectin mcg/kg	# Dogs/ Treatment	Treatment Days PI	Necropsy Mos PI	Number of Dogs With Adult Worms Found	# Worms Range	Percent Efficacy
Vehicle control	7	45	8-1/2	7	17-40	--
3.3	7	45	8-1/2	0	--	100
6.0	7	45	8-1/2	0	--	100
12.0	7	45	8-1/2	0	--	100
25.0	7	45	8-1/2	0	--	100
50.0	7	45	8-1/2	0	--	100

PI = post infection

ARS 11244
(Induced Infections; with ~50 larvae/dog)

Treatment Ivermectin mcg/kg	# Dogs/ Treatment	Treatment Days PI	Necropsy Mos PI	Number of Dogs With Adult Worms Found	# Worms Range	Percent Efficacy
Vehicle control	8	45	8-1/2	8	31-40	--
3.3	8	45	8-1/2	1	2	>99
6.0	8	45	8-1/2	0	--	100
12.0	8	45	8-1/2	1	1	>99
25.0	8	45	8-1/2	0	--	100
50.0	8	45	8-1/2	0	--	100

PI = post infection

ARS 10855
(Induced Infections; with ~50 larvae/dog)

Treatment Ivermectin mcg/kg	# Dogs/ Treatment	Treatment Days PI	Necropsy Mos PI	Number of Dogs With Adult Worms Found	# Worms Range	Percent Efficacy
Vehicle control	7	60	8-1/2	7	1-34	--
3.3	7	60	8-1/2	3	2, 2, 16	89.9
6.0	7	60	8-1/2	0	--	100
t12.0	7	60	8-1/2	1	5	97.2
25.0	7	60	8-1/2	0	--	100
50.0	7	60	8-1/2	0	--	100

PI = post infection

Table 4: Numbers of dogs in clinical trials by treatment.

Trial	Ivermectin	Control	Total
10641	124	31	155
10837	116	30	146
10943	109	23	132
10860	90	27	117
10861	92	31	123
10862	89	25	114
11093	81	27	108
TOTAL	701	194	895

IV. HUMAN FOOD SAFETY

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

Human Safety related to possession, handling, and administration:
Labeling contains adequate caution statement

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrated that HEARTGARD^{30} Tablets when used under the labeled conditions of use are safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because all dogs should be tested and treated for existing heartworm infection prior to starting treatment with HEARTGARD^{30} in a prevention program.

VI. LABELING (Attached)

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

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.