Approval Date: July 3, 1989

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-886

B. Sponsor

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

C. Proprietary Name

HEARTGARD-30 Chewables

D. Established Name

ivermectin

E. Dosage Form

The ingredients of HEARTGARD-30 Chewables are formulated into palatable, meat based chewable cubes. Three dosage sizes are available for dogs of different weight classes.

F. Dosage Regimen

HEARTGARD-30 Chewables supply a minimum of 6.0 mcg ivermectin per kg (2.72 mcg/lb) of body weight when given at the following recommended dose levels:

Dog Weight	Chewables Per Month	Ivermectin Content
Up to 25 lb	1	68 mcg
26 to 50 lb	1	136 mcg
51 to 100 lb	1	272 mcg

Give dogs heavier than 100 lb the appropriate combination of these sizes.

G. Route of Administration

HEARTGARD-30 Chewables are orally administered at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying heartworm larvae, are active.

H. Indication

For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) up to a month after infection.

II. EFFECTIVENESS

The New Animal Drug Application for ivermectin chewables contains data demonstrating that the product is the pharmacological equivalent of HEARTGARD-30 tablets and thus is also effective in the prevention of canine heartworm disease when given monthly at dose levels of at least 6 mcg of ivermectin per kg of body weight.

For additional information on efficacy studies for ivermectin in dogs refer to the Freedom of Information Summary, NADA 138-412 (52 FR 11041, 11042, 4/7/87).

Bioavailability

A bioavailability trial was conducted at Research Triangle Institute in Research Triangle Park, North Carolina. Sixteen non-pregnant adult female Beagles, with no history of a tendency to vomit, were selected for the trial. All dogs received one ivermectin chewable and one ivermectin tablet in a two-period crossover design. Radio-labeled ivermectin was used in both formulations. Treatments were separated by 42 days. No other medications were given.

Dogs were dosed orally and were carefully observed for emesis for 4 hours after each dosing. All dogs accepted and retained both the chewable and tablet formulations. Ivermectin was given at 6 mcg/kg, the lowest level that would be administered following label directions.

Blood samples (5 ml) were taken from each dog at Hour -24, and following each treatment at Hours 1,2,3,4,6,10,and 24, and at Days 2,3,5,7,10, and 14 (i.e., Hours 48, 72, 120, 168, 240 and 336). Three additional blood samples (at Hours 8, 12 and 15) were collected following the second treatment to define more precisely the radioactivity peak. Blood was centrifuged and plasma samples were frozen immediately for subsequent assay.

Two or 3 aliquots from each plasma sample were analyzed for total radioactivity in a scintillation spectrometer. The recovery of tritium from tritiated ivermectin was ð97%. Radioactivity counts per minute were converted to ivermectin ng-eq/g plasma using the specific activity of [3H]-ivermectin standards. Statistical analysis of area under the curve and of the natural logarithm of peak ivermectin concentration used an ANOVA for a two-period crossover design; plasma ivermectin concentration data were transformed using natural logarithms and analyzed using a repeated measures ANOVA. There were no significant Period or Sequence (i.e., Period x Formulation) effects for any variable analyzed.

The bioavailability of the two formulations was similar although not identical. Area under the curve was 22% greater for the chewable formulation than for the tablet (pÐ0.03); peak ivermectin plasma concentration was comparable for both formulations (p ð.05). Mean time-to-peak ivermectin plasma concentration was longer for the chewable formulation than for the tablet, but for both formulation, peak plasma concentrations were reached by 10 hours for 15 of the 16 dogs. Considering these results, a medical determination was made that the chewable formulation would provide comparable efficacy to the tablet.

Conclusion

Ivermectin has been shown to be effective in preventing heartworm disease in dogs at dose levels of 6 mcg/kg and higher. HEARTGARD-30 tablets are a dosage form of ivermectin which has been approved for use in this regard (NADA 138-412). Because the tablet and

chewable dosage forms have been shown to be pharmacokinetically similar and the chewables are as bioavailable to dogs as the tablets, HEARTGARD-30 Chewables are effective in preventing canine heartworm disease with a minimum monthly dose of 6 mcg ivermectin/kg body weight.

III. ANIMAL SAFETY

For additional information on safety studies for ivermectin in dogs refer to the Freedom of Information Summary, NADA 138-412.

Field Trials

The acceptability and safety of the chewable formulation were tested in four similar controlled field trials. The investigators are listed below:

Investigator	Location
Dr. Mark W. Coleman	Gainesville, Florida
Dr. Kenneth E. Acre	Winter Park, Florida
Dr. John W. Huigenbos	Ontario, Canada
Dr. Robert S. Blakely	Canterville, Illinois

Three hundred eighty-four client-owned dogs were enrolled in these trials. The dogs were maintained at home and their usual routines were maintained including treatment with a wide variety of commonly used animal health products. The owners administered the assigned trial medications, made observations, and kept records. The investigators examined the dogs at the start of the trial and provided routine veterinary care. In two of the trials, dogs were brought back to the clinics for follow-up examinations after 4 to 6 months. Of the 384 dogs, 255 received monthly treatment with ivermectin chewables according to the recommended dosage schedule. Control dogs received monthly treatment with HEARTGARD-30 tablets, or daily treatment with Filaribits® and monthly placebo (ALPO Beef Bites(TM)). Most of the dogs received 3 to 6 doses of monthly trial medication.

All dogs (except pups too young to require testing) were initially confirmed to be negative for heartworm, and all dogs brought back to the clinics for re-examination (in 2 trials) after 4 to 6 months were negative for heartworm. Test methods used were a Modified Knott or Difil-Test® (Evsco) and an antigen test.

The age range of dogs included in the trials was from 4 weeks to 14 years old and included 21 pups 14 weeks old or younger. There were 83 breeds, varieties or types of dogs, and 170 owners participated. One bitch whelped and another was bred and whelped while on HEARTGARD-30 Chewable treatment. Fifteen dogs did not complete the field trials for reasons unrelated to treatment.

No adverse reactions were attributed to treatment with ivermectin chewables. The most common observations were vomiting and diarrhea, and these were observed with lower incidence among dogs receiving ivermectin chewables than among those in either control group. One dog consumed 16 X 272 mcg ivermectin chewables at one time (resulting in a dose of 152 mcg/kg) and no untoward signs were observed.

Other observations included dermatoses of various etiologies. Three dogs on ivermectin chewables and three dogs on HEARTGARD-30 tablets were lethargic or sluggish. Two dogs were bitten by snakes and one of these dogs died; two dogs were hit by cars and one died.

A number of other unrelated observations were recorded, including: nephritis, cystitis, tachycardia, weight loss, coughing, protein losing enteropathy, tracheobronchitis, heart murmur, lump on shoulder, *Sarcoptes* infestation, chronic hip pain, sprained shoulder, throat infection, chewing on hip, and pharyngeal abscess.

More than 97% of the dogs on study accepted all doses of the ivermectin chewables. Owners of the 6 dogs which rejected the chewable on one or more occasions generally dosed their dogs by putting the ivermectin chewable in the dog's mouth as they would a swallow tablet. Comparative acceptability scores were best for dogs receiving the ivermectin chewables.

Palatability

In order to demonstrate the palatability and acceptability of the chewable formulation, a total of 91 dogs were used in a trial. Dogs were offered one chewable containing 85 to 112 mcg of ivermectin; owners were not given special instructions on how to administer the chewable, but rather, offered the chewable "free choice". Acceptance or rejection of the product, as well as any reactions, was recorded by owners who also made their own comments on the formulation.

More than 93% of the trial dogs consumed their ivermectin chewable when offered, 5 did not consume it and 1 ate half. No adverse reactions were observed after administration of the chewables. Comments concerning acceptability were generally very favorable. Twenty-four owners (26 dogs) remarked that their dogs were usually finicky, fussy, or hard to medicate but accepted the ivermectin chewable. Many breeds were included in the trial; the smallest dogs were two, 9-week old pups weighing 2.7 lb and 3 lb, respectively.

Conclusion

The safety and efficacy of ivermectin in dogs have been established in trials included in a previous submission (HEARTRGARD-30 tablets, NADA 138-412). Information on these studies is included in the Freedom of Information Summary for this previously approved product.

Demonstration of the safety and acceptability of ivermectin chewables in dogs was found in the 4 field trials conducted using 384 dogs. Ivermectin chewables were given monthly, according to the recommended label direction, to 255 of these dogs; most dogs received 3 to 6 doses. No adverse reactions attributable to ivermectin were observed.

IV. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residue residues in food, were not required for approval of this NADA. This product is labeled as a prescription drug for use only on dogs which are non-food animals.

Human safety relative to possession, handling, and administration: Labeling contains adequate caution statement.

Labeling states: Keep this and all drugs out of reach of children.

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 Chewables 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 in a prevention program.

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.