I. GENERAL INFORMATION

NADA Number: 141-078

Sponsor: Merck Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000
126 E. Lincoln Ave.
Rahway, New Jersey 07065-0914

Accepted Name: ivermectin

Trade Name: HEARTGARD™ for Cats

Marketing Status: A prescription (Rx) product which carries the following caution statement: "Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian."

II. INDICATIONS FOR USE

HEARTGARD™ for Cats is indicated for the prevention of feline heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis)* for a month (30 days) after infection, and for the removal and control of adult and immature (L_4) hookworms (*Ancylostoma tubaeforme* and *A. braziliense*).

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

The ingredients in HEARTGARD™ for Cats are formulated in a palatable beef-based chewable in two sizes for cats of different weight classes. The chewables are to be administered orally at monthly intervals during the mosquito (vector of *D. immitis*) season, and provide a minimum of 24 mcg ivermectin per kg of body weight (10.9 mcg/lb) when given as follows:

Cat Weight		Ivermectin
kg	lb	
up to 2.3	up to 5	55 mcg
2.3 to 6.8	5 to 15	165 mcg

For cats over 6.8 kg (15 lb) use the appropriate combination of chewables.

HEARTGARD™ for Cats is recommended for use in cats 6 weeks of age and older.

IV. EFFECTIVENESS

A. Dose Establishment

The dose was selected based on efficacy against adult *A. tubaeforme* which proved to be the dose-limiting parasite. In all efficacy trials, the percent efficacy

was calculated for each treatment group as the Control Geometric Mean minus the Treated Geometric Mean divided by the Control Geometric Mean X100.

1. Hookworm Dose Determination Study: ASR 13872

    a. Investigators: Dr. K. Todd and Dr. A. Paul, Univ. of Illinois, Urbana, Illinois

    b. Study design:

        1) Purpose: To determine the effective dose of ivermectin chewables against adult hookworms

        2) Test animals: 32 cats (17 male, 15 female), 10 weeks to 7 months of age, 8 per group

        3) Control: Vehicle chewables comprised of formulation excipients without active ingredient

        4) Diagnosis: Cats were experimentally infected with infective larvae of *Ancylostoma tubaeforme* 22 days before treatment so that the infection was in the adult stage at the time of treatment.

        5) Dosage form: Chewables

        6) Route of administration: Oral

        7 Dosages: 0, 12, 24, and 36 mcg/kg, tailored to body weight

        8) Duration of study: Cats were necropsied on Day 7

        9) Pertinent parameters measured: Worm counts at necropsy

    c. Results: Efficacy of ivermectin against adult *A. tubaeforme* was 83.8%, 99.3% and 99.6% at 12, 24, and 36 mcg/kg, respectively. The dose plateaus at 24 mcg/kg.

    d. Conclusion: 24 mcg/kg was selected as the dose of ivermectin providing >99% control of adult hookworms in cats

    e. Adverse reactions: No adverse reactions were observed.

2. Heartworm Dose Determination Study: ASR 13660

    a. Investigator: Dr. J. McCall, TRS Laboratories Inc., Athens, Georgia

    b. Study design:

        1) Purpose: To determine the effective dose of ivermectin chewables for preventing the development of heartworms (*Dirofilaria immitis)*

        2) Test animals: 40 cats (20 male, 20 female), 8 to 8.5 months of age, 8 per group

        3) Control: Vehicle chewables comprised of formulation excipients without active ingredient

        4) Diagnosis: Cats were experimentally infected with infective larvae of *D. immitis* 30 days before treatment (cats in one group were infected 45 days before treatment)

5) Dosage form: Chewables

6) Route of administration: Oral

7) Dosages: 0, 12, 24, and 36 mcg/kg, tailored to body weight; administered 30 days after infection; and 12 mcg/kg, administered 45 days after infection (one group)

8) Duration of study: Cats were necropsied on Day 150

9) Pertinent parameters measured: Worm counts at necropsy

c. Results: Ivermectin was 100% effective at all dose levels in preventing the development of *D. immitis*.

d. Conclusion: Ivermectin administered at 12, 24, and 36 mcg/kg body weight prevents the development of *D. immitis*.

e. Adverse reactions: No adverse reactions were observed.

B. Dose Confirmation

1. Heartworm Dose Confirmation Studies: ASR 14324 and ASR 14328

a. Investigators: Dr. J. McCall, TRS Laboratories Inc., Athens, Georgia (ASR 14324); and Dr. L. Cruthers, Professional Laboratory and Research Services Inc., Corapeake, North Carolina (ASR 14328)

b. Study design:

1) Purpose: To confirm the efficacy of ivermectin chewables at 24 mcg/kg in preventing the development of *Dirofilaria immitis*

2) Test animals: ASR 14324: 20 cats (10 male, 10 female), 6.2 to 7.5 months of age, 10 cats per group; ASR 14328: 20 cats (10 males, 10 females), approximately 8 months of age, 10 cats per group

3) Control: Vehicle chewables comprised of formulation excipients without active ingredient

4) Diagnosis: Cats were experimentally infected with infective larvae of *D. immitis* 30 days before treatment

5) Dosage form: Chewables

6) Route of administration: Oral

7) Dosage: 24 mcg/kg, tailored to body weight

8) Duration of study: Cats were necropsied on Day 151

9) Pertinent parameters measured: Worm counts at necropsy

c. Results: Ivermectin was 100% effective in preventing the development of *D. immitis*.

d. Conclusion: Ivermectin administered at the minimum recommended dose of 24 mcg/kg prevents the development of *D. immitis*

e. Adverse reactions: No adverse reactions were observed.

2. Hookworm Dose Confirmation Studies: ASR 14015 and ASR 14166

   a. Investigators: Dr. E. Roberson, TRS Laboratories, Inc., Athens, Georgia (ASR 14015); and Dr. A. Paul, University of Illinois, Urbana, Illinois (ASR 14166)

   b. Study design:

      1) Purpose: To confirm the efficacy of ivermectin chewables at 24 mcg/kg against immature (L_4) hookworms

      2) Test animals: ASR 14015: 14 cats (7 males, 7 females), 4.8 to 5 months of age, 7 per group; ASR 14166: 14 cats (7 males, 7 females), 15 to 16 weeks of age, 7 per group

      3) Control: Vehicle chewables comprised of formulation excipients without active ingredient

      4) Diagnosis: Cats were experimentally infected with infective larvae of *Ancylostoma tubaeforme* and *A. braziliense* eight days before treatment so that the infections were in the fourth larval stage at the time of treatment

      5) Dosage form: Chewables

      6) Route of administration: Oral

      7) Dosage: 24 mcg/kg, tailored to body weight

      8) Duration of study: Cats were necropsied on either Day 21 (ASR 14015) or Day 14 (ASR 14166)

      9) Pertinent parameters measured: Worm counts at necropsy

   c. Results: The efficacy of ivermectin in ASR 14015 against L_4 *A. tubaeforme* was 97.3%, and against L_4 *A. braziliense* was 100%. The efficacy of ivermectin in ASR 14166 against L_4 *A. tubaeforme* was 97.8%, and against L_4 *A. braziliense* was 98.9%.

   d. Conclusion: Ivermectin administered at the minimum recommended dose of 24 mcg/kg is effective against infections of immature (L_4) *A. tubaeforme* and *A. braziliense*

   e. Adverse reactions: No adverse reactions were observed.

3. Hookworm Dose Confirmation Study: ASR 14612

   a. Investigator: Dr. M. Drag, Merck Missouri Farm, Fulton, Missouri

   b. Study design:

      1) Purpose: To confirm the efficacy of ivermectin chewables, in two different batches, using different methods of administration, in removing and controlling adult hookworm infections

      2) Test animals: 48 cats (24 males, 24 females), 11 to 13 months of age, 8 per group

      3) Control: Vehicle chewables comprised of formulation excipients without the active ingredient

4) Diagnosis: Cats were experimentally infected with infective larvae of *Ancylostoma tubaeforme* and *A. braziliense* 33 or 34 days before treatment, so that the hookworms were in the adult stage at the time of treatment. Patency was confirmed by fecal egg counts.

5) Dosage form: Chewables

6) Route of administration: Oral

7) Dosage: 24 mcg/kg: the ivermectin groups were as follows:

Trt 2: Ivermectin Batch 014, tailored to 24 mcg/kg, quartered and manually dosed

Trt 3: Ivermectin Batch 017, tailored to 24 mcg/kg, quartered and manually dosed

Trt 4: Ivermectin Batch 014, tailored to 24 mcg/kg, quartered and manually dosed, if not voluntarily consumed

Trt 5: Ivermectin Batch 014, tailored to 24 mcg/kg, crumbled and mixed with canned food before administration

Trt 6: Ivermectin Batch 014, ≥ 24 mcg/kg, quartered and manually dosed, if not voluntarily consumed

8) Duration of study: Cats were necropsied on Day 7

9) Pertinent parameters measured: Worm counts at necropsy.

c. Results: Efficacy of ivermectin against adult *A. tubaeforme* was 94.9%, 100%, 98.3%, 100% and 100%, respectively, in Treatment Groups 2, 3, 4, 5, and 6. Efficacy of ivermectin against *A. braziliense* was >99% to 100% in all five treatment groups. Twenty-four of the 48 cats had remnants of the chewables in their feces at 24 hours post-treatment and 4 cats passed remnants in the feces at 48 hours post-treatment. No remnants were detected at 72 hours.

d. Conclusion: Ivermectin administered at the minimum dose of 24 mcg/kg, in two different batches using different methods of administration, (quartered and manually dosed, offered free choice, and quartered and then mixed with food), is effective against infections of adult *A. tubaeforme* and *A. braziliense*. The appearance of chewable remnants in the feces within 48 hours of administration did not affect efficacy.

e. Adverse reactions: No adverse reactions were observed.

4. Hookworm Dose Confirmation Study: ASR 14340

a. Investigator: Dr. J. McCall, TRS Laboratories Inc., Athens, Georgia

b. Study design:

1) Purpose: To confirm the efficacy of ivermectin chewables at 24 mcg/kg against hookworms

2) Test animals: 14 cats (6 males, 8 females), 5 to 120 months of age, 7 per group

3) Control: Vehicle chewables comprised of formulation excipients without active ingredient

4) Diagnosis: All cats had natural hookworm infections as determined by fecal egg counts on Day -1

5) Dosage form: Chewables

6) Route of administration: Oral

7) Dosage: ≥24 mcg/kg, as per label

8) Duration of study: Cats were necropsied on Day 7

9) Pertinent parameters measured: Worm counts at necropsy

c. Results: Efficacy of ivermectin was 100%

d. Conclusion: Ivermectin administered at the minimum recommended dose of 24 mcg/kg is effective against natural infections of hookworms

e. Adverse reactions: No adverse reactions were observed.

5. Other Confirmation Studies

Five trials (ASR 12914, 13204, 13210, 13221, and 14560) were conducted in cats with experimental or natural infections of adult *A. tubaeforme* to confirm the efficacy of ivermectin at 24 mcg/kg. Three of these trials also included infections of adult *A. braziliense.* Thirty-three cats were treated with ivermectin chewables and 33 with vehicle. The percent efficacy achieved in each study is shown below.

Parasite	Trial Number	Percent Efficacy
Ancylostoma tubaeforme (induced infections, adult worms)	12914	99.6
	13210	100
	13204	90.7
	14560	71.9
Ancylostoma tubaeforme (natural infections)	13221	100
Ancylostoma braziliense (induced infections, adult worms)	13204	92.8
	13221	99.8
	14560	52.2

Combined efficacy for these five trials is 94.4% against *A. tubaeforme* and 94.9% against *A. braziliense*.

C. Field Investigations

A waiver of criteria for an adequate and well-controlled field investigation specified in 21 CFR 514.111(a)(5)(ii) was granted by CVM. Specifically, the criteria in paragraph (a)(5)(ii)(*a*)(*4*) for a comparison of the results of the treatment with a control was waived for the field investigations with ivermectin for the prevention of heartworm disease in cats caused by *Dirofilaria immitis* (see attachment 1).

1. Field Trials under Protocol 3784: Four trials (ASR 14007, 14009, 14010, and 14014) were conducted under this protocol.

   a. Investigators:

Trial 14007	Dr. K. Acre	Altamonte Veterinary Hospital Altamonte Springs, Florida
Trial 14009	Dr. M. Dzimianski	South Jackson Veterinary Services Nicholson, Georgia
Trial 14010	Dr. T. Clekis	Animal Hospital of St. Petersburg St. Petersburg, Florida
Trial 14014	Dr. T. McArthur	Altamaha Animal Clinic Vidalia, Georgia

   b. Study design:

      1) Purpose: To confirm the safety, efficacy and acceptability of ivermectin chewables at use level for the removal and control of hookworms under field conditions.

      2) Test animals: Cats ranged in age from 10 weeks to 12 years.

	Males	Females	Total
Trial 14007	4	6	10
Trial 14009	11	13	24
Trial 14010	20	21	41
Trial 14014	7	14	21
Total	42	54	96

      3) Control: Vehicle chewables comprised of formulation excipients without active ingredient.

      4) Diagnosis: Natural infections of hookworms confirmed by fecal egg counts. Before being placed on trial, cats over 4 months old were tested for adult heartworm antigen and found negative.

      5) Dosage form: Chewables

      6) Route of administration: Oral

      7) Dosage: Recommended dose of ≥ 24 mcg/kg, as per label, monthly for 3 months

      8) Pertinent parameters measured: Fecal samples were examined for intestinal nematode eggs approximately 7 to 14 days after each of three monthly treatments. Study reports were compiled from owners' and investigators' records.

   c. Results: Of 96 cats enrolled, 66 had hookworm infections and had at least one follow-up examination. Numbers of cats positive at each examination were:

	Pre-Test	7 to 14 days	37 to 44 days	52 to 74 days
Ivermectin	48/48	4/48	1/45	0/44
Control	18/18	9/18	11/18	11/17

A variety of medications were administered to cats during the study, including vaccines, flea treatments, antimicrobials, sedatives, anesthetics and steroid preparations. Owners or veterinarians successfully administered 99.6% of the ivermectin chewables (free choice, in food, or manually).

d. Conclusion: Ivermectin, administered in this chewable dosage form, is acceptable to cats and is safe and effective in removing and controlling hookworm infections under field conditions when administered monthly at the recommended dose of ≥ 24 mcg/kg.

e. Clinical Observations: See page 13

2. Field Trials under Protocol 2876: Seven trials (ASR 13138, 13211, 13212, 13213, 13217, 13218, and 13339) were conducted under this protocol.

a. Investigators:

Trial 13138	Dr. R. Blakely	Central Hospital for Animals Carterville, Illinois
Trial 13211	Dr. R. Lange	Lange Animal Hospital Knoxville, Tennessee
Trial 13212	Dr. M. Coleman	Suburban Animal Hospital Gainesville, Florida
Trial 13213	Dr. R. Brady	Westbury Animal Hospital Houston, Texas
Trial 13217	Dr. T. Greene	Greene Veterinary Clinic Livonia, Louisiana
Trial 13218	Dr. K. Acre	Howell Branch Animal Hospital Winter Park, Florida
Trial 13339	Dr. T. Clekis	Animal Hospital of North Charleston Charleston, South Carolina

b. Study design:

1) Purpose: To confirm the safety, efficacy and acceptability of ivermectin chewables at use level for the removal and control of hookworms and the prevention of heartworm disease under field conditions.

2) Test animals: Cats ranged in age from 6 weeks to 17 years.

	Males	Females	Total
Trial 13138	38	32	70
Trial 13211	32	30	62
Trial 13212	26	44	70
Trial 13213	37	35	72
Trial 13217	47	23	70
Trial 13218	31	36	67
Trial 13339	34	28	62
Total	245	228	73

3) Control: None (waiver granted, see attachment 1)

4) Diagnosis: Fifty-one cats had natural infections of hookworms, confirmed by fecal egg counts. Before being placed on trial, all cats ≥ 4 months old were tested for circulating microfilariae and adult heartworm antigen and found negative.

5) Dosage form: Chewables

6) Route of administration: Oral

7) Dosage: Recommended dose of ≥ 24 mcg/kg, as per label, monthly for 5 months

8) Pertinent parameters measured: Fecal samples were examined for intestinal nematode eggs before the first treatment and after the first, third and fifth doses. Blood for evaluation of microfilariae and adult heartworm antigen was obtained 6 months after the last treatment. Clinical study reports were compiled from owners' and investigators' records.

c. Results: Of 51 cats with hookworms, 46 had at least one follow-up fecal exam. Numbers of cats positive at each examination were:

	Pre-Test	Month 1	Month 3	Month 5
Ivermectin	46/46	2/46	1/39	1/38

Results from the 373 cats that completed the study and were available for final heartworm tests confirmed the efficacy of ivermectin. One cat tested heartworm antigen positive at month 11 of the study; however, because the available antigen tests were not highly reliable in detecting natural heartworm infections in cats, it is not clear exactly when this cat became infected. A variety of medications were administered to cats during the study, including vaccines, flea treatments, antimicrobials, sedatives, anesthetics and steroid preparations. Owners or veterinarians successfully administered 98% of the ivermectin chewables (free choice, in food, or manually).

d. Conclusion: Ivermectin, administered in this chewable dosage form, is acceptable to cats and is safe and effective in removing and controlling hookworm infections under field conditions and in preventing heartworm disease when administered monthly at the recommended dose of ≥ 24 mcg/kg.

e. Clinical Observations: See page 13

3. Field Trials under Protocol 2999: Three trials (ASR 13224, 13225 and 13468) were conducted in kittens under this protocol.

a. Investigators:

Trial 13224	Dr. T. Clekis	Animal Hospital of North Charleston Charleston, South Carolina
Trial 13225	Dr. M. Coleman	Suburban Animal Hospital Gainesville, Florida
Trial 13468	Dr. R. Hawe	Alexandria Animal Hospital Alexandria, Virginia

b. Study design:

1) Purpose: To confirm the safety, efficacy and acceptability against hookworms of ivermectin chewables at use level in kittens from 5 to 24 weeks old under field conditions.

2) Test animals:

	Males	Females	Total
Trial 13224	15	17	32
Trial 13225	9	7	16
Trial 13468	19	5	24
Total	43	29	72

3) Control: Vehicle chewables were comprised of formulation excipients without active ingredient

4) Diagnosis: Two kittens in the ivermectin group had natural infections of hookworms prior to treatment, confirmed by fecal egg counts.

5) Dosage form: Chewables

6) Route of administration: Oral

7) Dosage: Recommended dose of ≥ 24 mcg/kg, monthly for 3 months

8) Pertinent parameters measured: Fecal samples were examined for intestinal nematode eggs before the first treatment and approximately 7 to 14 days after the third (last) monthly dose. Study reports were compiled from owners' and investigators' records.

c. Results: Only two of the ivermectin-treated kittens had hookworms at the start of the trial and both were negative at the final fecal examination; the rest of the kittens from both the ivermectin and control groups were hookworm negative at study initiation and remained hookworm-free throughout the trial. A variety of medications were administered to kittens during the study, including vaccines, flea treatments, antimicrobials, sedatives, anesthetics and steroid preparations. Owners or veterinarians successfully administered 97% of the ivermectin chewables (free choice, in food, or manually).

d. Conclusion: Ivermectin, administered in this chewable dosage form, is acceptable to kittens and is safe when administered at the recommended dose of ≥ 24 mcg/kg.

e. Clinical Observations: See Page 13

4. Field Trials under Protocols 2875 and 2878: Five trials were conducted in the USA under protocol 2875 (ASR 13170, 13172, 13186, 13188 and 13190) and one in Canada under protocol 2878 (ASR 13203).

a. Investigators:

Trial 13170	Dr. K. Blaicher	Animal Medical Group Plainfield, New Jersey
Trial 13172	Dr. B. Levine	Toms River Veterinary Hospital Toms River, New Jersey
Trial 13186	Dr. S. McDonough	Cat Hospital of Philadelphia Philadelphia, Pennsylvania
Trial 13188	Dr. A. Ellis	River Cove Animal Hospital Williston, Vermont
Trial 13190	Dr. D. Lukof	Harleysville Veterinary Hospital Harleysville, Pennsylvania
Trial 13203	Dr. C. MacKay	MacKay Animal Clinic Whitby, Ontario, Canada

b. Study design:

1) Purpose: To confirm the safety and acceptability of ivermectin chewables at use level under field conditions.

2) Test animals: 377 cats (194 males and 183 females) were included in the trials: 302 cats in the USA, 75 cats in Canada. The cats ranged in age from 8 weeks to 17 years.

3) Control: Vehicle chewables were comprised of formulation excipients without active ingredient

4) Dosage form: Chewables

5) Route of administration: Oral

6) Dosage: Recommended dose of ≥ 24 mcg/kg, monthly for 5 months

c. Results: A variety of medications were administered to cats during the study; these included vaccines, flea treatments, antimicrobials, sedatives, anesthetics and steroid preparations. In the USA, owners or veterinarians successfully administered 96% of the ivermectin chewables, and in Canada, 97.5% (free choice, in food, or manually).

d. Conclusion: Ivermectin, administered in this chewable dosage form, is acceptable to cats and is safe when administered at the recommended dose of ≥ 24 mcg/kg.

e. Clinical Observations: See below.

Clinical Observations from all 4 Field Investigations: In all clinical trials, observations reported within 24 hours of treatment included vomition in ≤ 0.3% and diarrhea in ≤ 0.2% of the doses administered. There were no statistical differences between Heartgard™ for Cats and the product vehicle (control) for these observations.

Clinical Observation	Vehicle-Treated Cats (990 doses)	Ivermectin-Treated Cats (3,252 doses)
Vomiting	0.30%	0.28%
Diarrhea	0.20%	0.09%

D. Other Studies

Trials 14282 and 14430 showed that feeding of cats and breaking of chewables reduced the variability in absorption of ivermectin and reduced the incidence of remnants of chewables in the feces.

Trial 14282: Twelve cats were used in this crossover design study. Six cats received a crumbled chewable on day 0 and a whole chewable on day 14 while the remaining 6 cats received the whole chewable on day 0 and the crumbled chewable on day 14. Blood was collected after each treatment for evaluation of ivermectin levels. Cats given the crumbled chewable had a higher absorption of ivermectin than those given the chewable administered whole.

Trial 14430: Twenty-four cats were divided into 4 groups and received whole and crumbled ivermectin chewables while fasted and while fed *ad libitum*, as follows:

Group	Feeding Schedule	How Fed
1	Day 0 -- Fed *Ad libitum* Day 6 -- Fasted	Whole
2	Day 0 -- Fasted Day 6 -- Fed *Ad libitum*	Whole
3	Day 0 -- Fed *Ad libitum* Day 6 -- Fasted	Crumbled
4	Day 0 -- Fasted Day 6 -- Fed *Ad libitum*	Crumbled

All feces produced for 72 hours after treatment were collected and visually inspected for evidence of lack of disintegration of the chewable. Six of the 24 cats had chewable fragments in the feces when fed *ad libitum* compared to 21 of the 24 cats when fasted. Of the six cats that had chewable fragments when fed *ad libitum*, 4 were with the whole chewable and 2 were with the crumbled chewable

V. ANIMAL SAFETY

Seven controlled studies were conducted in cats to address the tolerance and safety of ivermectin chewables. Studies were specifically designed to evaluate safety of ivermectin administered at exaggerated doses in breeding queens and toms, in adult cats, in kittens, and at the recommended dose in cats with heartworm microfilariae.

A. Pivotal Studies

1. Six-month Tolerance Study in Kittens: ASR 14034

   a. Investigator: Dr. E. Schwartz, White Eagle Toxicology Laboratories, Inc., Doylestown, Pennsylvania

   b. Study design:

      1) Purpose: To demonstrate tolerance of growing kittens to ivermectin chewables at 1X, 3X, or 5X the label dose at 28-day intervals for 8 doses

      2) Test animals: 28 6-week-old kittens (13 males, 15 females), 7 kittens per group

      3) Dosage form: Chewables

      4) Dosages: Each kitten was treated 8 times at 28-day intervals. Kittens received vehicle, or ivermectin at 1X (≥24 mcg/kg), at 3X (≥72 mcg/kg), or at 5X (≥120 mcg/kg) the recommended dose.

      5) Route of administration: Oral

      6) Test duration: 203 days

      7) Pertinent parameters measured: A detailed physical examination was conducted on each kitten before Day 0 and on Day 202. Kittens were weighed before each treatment day and on Day 202. On each of the eight treatment administration days, each kitten was observed hourly for 6 hours and approximately 24 hours after treatment for any signs of reactions. On the treatment days, detailed clinical evaluations were performed at 3 and 6 hours after treatment and daily thereafter for 7 days. Hematology and blood chemistry were assessed before Day 0 and on Days 61, 120, and 203. Histopathology: Kittens were necropsied on Day 203.

   c. Results: There were no statistically significant effects of treatment on heart rate, respiration, temperature, and final weight gain; though cats in the high dose group had statistically significantly less weigh gain to Day 83. One cat in the high dose group vomited and a second cat showed diarrhea within 24 hours of the first dose.

   d. Conclusions: Ivermectin, administered in this chewable dosage form, is safe when administered to kittens at the label dose of ≥24 mcg/kg body weight.

2. Reproduction Study in Male Cats: ASR 13234

   a. Investigator: Dr. J. Laveglia, Food and Drug Research Laboratories, Waverly, New York

b. Study design:

1) Purpose: To demonstrate the safety of ivermectin chewables to breeding male cats at 4X the frequency and at 3X the label dose of ≥ 24 mcg/kg.

2) Test animals: 14 adult male cats, 7 per group, and 28 adult female cats, 14 per group. Cats had sired or queened at least two litters each.

3) Dosage form: Chewables

4) Dosages: Male cats in the control group were offered three vehicle chewables daily throughout the study while males in the ivermectin group received at least 3X the minimum recommended dose of 24 mcg/kg once per week. Three vehicle chewables were offered to the cats on non-treatment days. Chewables were administered to each male cat in the ivermectin group 11 times at 7-day intervals before being bred to each of two female cats. Female cats were not treated. Weekly treatment of the males continued until the parturition of the females to which they were mated or until termination of the study.

5) Route of administration: Oral

6) Test duration: 18 months

7) Pertinent parameters measured: Males received a physical examination before the start of the stud^y and at the end of the study; they were observed daily and weighed weekly. Within 48 hours of parturition, each kitten was examined and weighed. Kittens were examined and weighed again at weaning.

c. Results: Six of the seven control males and all seven ivermectin-treated males mated. No adverse effects were noted in any treated male cats during the study. There were no statistically significant effects of treatment on birth weight or weaning weight of kittens, on numbers of litters with mortalities or abnormalities, on total litter size, percent born alive and percent weaned, or on weight gains of male cats.

Test Group	Litter Size[1]	Percent Live Birth	Mean Birth Weight (grams)	Weaning Index[2]
Control	3.9	90%	109.3	91%
Ivermectin	3.25	74%	111.0	76%
Statistical Significance[3]	N.S.	N.S.	N.S.	N.S.

[1]Litter size was calculated as the total number of kittens divided by the number of pregnant queens. [2]Weaning Index was calculated as the number of kittens weaned divided by the number born alive X100.
[3] No statistically significant differences between treated and control groups.

d. Conclusion: Ivermectin, administered in this chewable dosage form, is safe when administered to breeding toms at the label dose of ≥24 mcg/kg body weight.

3. Reproduction Study in Female Cats: ASR 13235

   a. Investigator: Dr. J. Laveglia, Food and Drug Research Laboratories, Waverly, New York

   b. Study design:

      1) Purpose: To demonstrate safety to breeding female cats given ivermectin chewables at least at 4X the frequency and at 3X the label dose of ≥ 24 mcg/kg

      2) Test animals: 36 adult female cats, 6 per group; and 6 adult male cats, 1 per group. Cats had queened or sired at least two litters each.

      3) Dosage form and route of administration: Chewables, administered orally

      4) Dosages: Each ivermectin-treated cat received at least 3X the minimum recommended dose of 24 mcg/kg at each administration. These cats were treated through all stages of organogenesis and lactation. Chewables were administered to each female cat in the ivermectin groups at least 5 times at 7-day intervals before being bred to the male cat assigned to its replicate. Male cats were not treated. During gestation, female cats of the four ivermectin treatment groups were treated at least at 3X the label dose every fourth day from Day 1, 2, 3, or 4 of gestation to Day 33, 34, 31, or 32 of gestation, respectively. Weekly treatment of the females resumed for the second half of gestation and continued through parturition and lactation until their kittens were weaned.

      5) Test duration: 13 months

      6) Pertinent parameters measured: Females received a physical examination at the start and end of the study; they were observed daily and weighed weekly. Within 48 hours of parturition, each kitten was examined and weighed. Kittens were observed daily; they were examined and weighed again at weaning.

   c. Results: Three females (1 control, 2 ivermectin-treated) failed to conceive. There were no statistically significant effects of treatment on birth weight or weaning weight of kittens, on proportions of litters with mortalities or abnormalities, on total litter size, percent born alive and percent weaned, or on weight of female cats.

Test Group	Litter Size[1]	Percent Live Birth	Mean Birth Weight (Grams)	Weaning Index[2]
Control	4.2	93.5%	123.3	95.3%
Ivermectin	3.5	89.5%	128.2	88.2%
Statistical Significance[3]	N.S.	N.S.	N.S.	N.S.

[1]Litter size was calculated as the total number of kittens divided by the number of pregnant queens. [2]Weaning Index was calculated as the number of kittens weaned divided by the number born alive X100.
[3] No statistically significant differences between treated and control groups.

d. Conclusion: Ivermectin, administered in this chewable dosage form, is safe when administered to breeding queens at the label dose of ≥24 mcg/kg body weight.

4. Reproduction Study in Male Cats: ASR 13952

a. Investigator: Dr. M. Gilman, Liberty Research, Inc., Waverly, New York

b. Study design:

1) Purpose: To demonstrate safety to breeding male cats given ivermectin chewables at 4X the frequency and at 3X the label dose of ≥ 24 mcg/kg.

2) Test animals: 20 adult male cats, 10 per group, and 40 adult female cats, 20 per group. Cats had sired or queened at least two litters each.

3) Dosage form and route of administration: Chewables, administered orally

4) Dosages: Male cats were given three whole vehicle or ivermectin chewables once per week. Each ivermectin-treated cat received at least 3X the minimum recommended dose of 24 mcg/kg at each administration. Each male cat was treated 10 times at 7-day intervals before being bred to each of two female cats. Female cats were not treated. Weekly treatment of the males continued until the parturition of the females to which they were mated or until termination of the study.

5) Test duration: 10 months

6) Pertinent: Males received a physical examination before the start of the study and at the end of the study; they were observed daily and weighed weekly. Within 48 hours of parturition, each kitten was examined for malformations and abnormalities. Kittens were weighed within 72 to 102 hours after birth and at weaning, as part of an overall physical examination.

c. Results: All males in both groups mated. No adverse effects were noted in any treated male cats during the study. There were no statistically significant effects of treatment on average birth weight or weaning weight of litters, on numbers of litters with mortalities or abnormalities, on total litter size and percent born alive, or on male weights. The percentage of kittens weaned was significantly ($p<0.05$) higher in the ivermectin-treated group than in the control group.

Test Group	Litter Size[1]	Percent Live Birth	Mean Birth Weight (grams)	Weaning Index[2]
Control	4.8	94%	157.6	86%
Ivermectin	3.9	89%	174.2	92%
Statistical Significance[3]	N.S.	N.S.	N.S.	N.S.

[1]Litter size was calculated as the total number of kittens divided by the number of pregnant queens. [2]Weaning Index was calculated as the number of kittens weaned divided by the number born alive X100.
[3] No statistically significant differences between treated and control groups.

d. Conclusion: Ivermectin, administered in this chewable dosage form, is safe when administered to breeding toms at the label dose of ≥24 mcg/kg body weight

5. Reproduction Study in Female Cats: ASR 13951

a. Investigator: Dr. M. Gilman, Liberty Research, Inc., Waverly, New York

b. Study design:

1) Purpose: To demonstrate safety to breeding female cats given ivermectin chewables at 4X the frequency and at 3X the label dose of ≥ 24 mcg/kg.

2) Test animals: 72 adult female cats, 6 per group, and 6 adult male cats, 1 per group. Cats had queened or sired at least two litters each.

3) Dosage form and route of administration: Chewables, administered orally

4) Dosages: Each female cat received three vehicle chewables (8 groups) or three ivermectin chewables (4 groups) once a week for four weeks before breeding began. Each ivermectin-treated cat received at least 3X the minimum recommended dose of 24 mcg/kg at each administration. These cats were treated through all stages of organogenesis and lactation. After breeding to the male cat assigned to its replicate, the female cats were treated at least at 3X every fourth day from Day 1, 2, 3, or 4 of gestation to Day 33, 34, 35, or 36 of gestation, respectively. Male cats were not treated. Weekly treatment of the females resumed for the second half of gestation and continued through parturition and lactation until their kittens were weaned.

5) Test duration: 12½ months

6) Pertinent parameters measured: Females received a physical examination before the start of the study and at the end of the study; they were observed daily and weighed weekly. If any abnormalities were observed during the daily observation then a physical examination was conducted. Within 48 hours of parturition, each kitten was examined for malformations and abnormalities. Kittens were weighed within 72 to 102 hours after birth and at weaning, as part of an overall physical examination.

c. Results: Thirteen females (10 controls and 3 ivermectin-treated) failed to conceive. There were no statistically significant effects of treatment on birth weight of kittens, on proportions of litters with mortalities or abnormalities, on total litter size, percent born alive and percent weaned, or on weight of female cats.

Test Group	Litter Size[1]	Percent Live Birth	Mean Birth Weight (grams)	Weaning Index[2]
Control	3.7	96%	175.5	95%
Ivermectin	3.9	96%	159.2	88%
Statistical Significance[3]	N.S.	N.S.	N.S.	N.S.

[1]Litter size was calculated as the total number of kittens divided by the number of pregnant queens. [2]Weaning Index was calculated as the number of kittens weaned divided by the number born alive X100.
[3] No statistically significant differences between treated and control groups

Mean weight at weaning was 591.4 and 544.3 g, respectively, for the control and ivermectin-treated kittens ($p<0.05$), but these means are within expected ranges for normal weaning weights for kittens. The mean weights at weaning in the four reproductive safety studies were similar:

Study No.	Mean weaning weight (g) of control kittens	Mean weaning weight (g) of ivermectin-treated kittens
13234	503.5	579.6
13235	531.5	580.3
13952	511.5	570.0
13951	591.4	544.3

d. Conclusion: Ivermectin, administered in this chewable dosage form, is safe when administered to breeding queens at the label dose of ≥24 mcg/kg body weight.

6. Safety Study in Microfilariae-Positive Cats: ASR 12671

   a. Investigator: Dr. J. McCall, TRS Laboratories, Inc., Athens, Georgia

   b. Study design:

      1) Purpose: To demonstrate safety of ivermectin chewables given to cats with patent infections of adult *Dirofilaria immitis*

      2) Test animals: 12 cats (7 male and 5 female), 7 to 12 months of age, 6 per group

      3) Dosage and route of administration: Cats were treated orally with ivermectin chewables to provide ivermectin at ≥ 24 mcg/kg, or with vehicle chewables

      4) Infection: Each cat was infected on Day -13 with 4 female and 1 to 4 male adult *D. immitis* via jugular venotomy

      5) Duration: 14 days

      6) Pertinent parameters measured: Clinical observations, hematology and clinical chemistry were recorded throughout the trial. Heartworms were recovered at necropsy on Day 14, and organ and tissue samples were examined histopathologically.

   c. Results: Live adult heartworms were recovered from all cats at necropsy. Circulating microfilariae were seen in both treatment groups from Day 0 through Day 9. However, on Days 11 and 14 there were no microfilariae in the ivermectin-treated cats, whereas 5 of 6 cats in the control cats were

microfilaremic on Day 11 and 2 of 6 were microfilaremic on Day 14. No adverse effects of treatment were observed.

d. Conclusion: Ivermectin, administered in this chewable dosage form, is safe when administered to cats with patent infections of *D. immitis* at the label dose of ≥24 mcg/kg body weight.

7. Drug Tolerance Study: ASR 12996

a. Investigator: Dr. M. Gilman, Hazleton-LRE, Kalamazoo, MI

b. Study design:

1) Purpose: To evaluate toxicity of ivermectin in cats

2) Test animals: 24 cats (12 male and 12 female), 7 months of age, 6 per group

3) Dosage and route of administration: Cats were given ivermectin tablets orally, to provide ivermectin at 750, 1000, or 4800 mcg/kg, or they were given vehicle tablets

4) Duration: 13 days

5) Pertinent parameters measured: Clinical observations were made before treatment and at 4.5 and 7.5 hours after treatment and on Days 1, 2, 3, 4, 5, 6, 9, and 12; all cats were observed daily. Hematology, clinical chemistry, and fecal examinations were performed before treatment and on Days 2, 8, and 12. At necropsy, gross and histopathological examinations were conducted.

c. Results: Typical signs of toxicosis consisted of exaggerated startle response, absence of pupillary light response, unsteady gait, incoordination, tremors, and recumbency. The no-effect-level for a single dose of ivermectin was established at 750 mcg/kg (30X the recommended minimum dose of 24 mcg/kg).

d. Conclusion: The toxic syndrome was established in these studies.

B. Corroborative Studies

The field trials conducted in support of this application are considered to be corroborative target animal safety studies.

VI.HUMAN SAFETY

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

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Section 514 of the implementing

regulations (Title 21 of the Code of Federal Regulations). The data demonstrate that HEARTGARD™ for Cats (ivermectin) when used under labeled conditions of use, is safe and effective for the prevention of feline heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis)* for a month (30 days) after infection, and for the removal and control of adult and immature (L_4) hookworms (*Ancylostoma tubaeforme* and *A. braziliense)*.

Labeling restricts this drug to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine the existence of hookworm and/or heartworm infections.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding are contained in an environmental assessment, which may be seen in the Docket Management Branch (HFA-305), Parklawn Building (Room 1-23), 12420 Parklawn Dr., Rockville, Maryland 20857.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

HEARTGARD™ for Cats is under patent numbers U.S. 4199569, expiring October 3, 1997.

VIII. APPROVED LABELING

Copies of facsimile labeling are attached to this document.

A. 10X Stadium tray

B. Tuck carton (55 µg)

C. Tuck carton (165 µg)

D. Blister card (55 µg)

E. Blister card (165 µg)

F. Wallet dispenser

G. Insert

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.