

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-189

**ProHeart[®] 6 (moxidectin) Sustained Release
Injectable for Dogs**

Sponsored by:

Fort Dodge Animal Health

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I. General Information

NADA Number: 141-189

Sponsor: Fort Dodge Animal Health
Division of American Home Products Corporation
800 Fifth Street NW
Fort Dodge, Iowa 50501

Generic Name: Moxidectin

Tradename: ProHeart[®] 6 (moxidectin) Sustained Release Injectable
for Dogs

Marketing Status: Rx: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

II. Indications for Use

ProHeart 6 is indicated for use in dogs six months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis*.

ProHeart 6 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum*) infections.

III. Dosage Form, Route of Administration and Dosage:

Dosage Form:

ProHeart 6 (moxidectin) is provided in two separate vials that require mixing prior to use. Vial 1 contains 10% moxidectin microspheres and Vial 2 contains a specifically formulated vehicle. Constitution of the moxidectin microspheres in Vial 1 with the vehicle in Vial 2 must be done precisely as directed in the product labeling. No other diluent should be used to constitute Vial 1. The constituted suspension is ready for administration 30 minutes after mixing.

Route of Administration:

The constituted product is intended for subcutaneous administration with an 18G or 20G hypodermic needle in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3.0 mL should be administered in a single site. The location(s) of each injection (left or right side) should be noted so that prior injection sites can be identified and the next injection can be administered on the opposite side.

Dosage:

The constituted product is administered at the dose of 0.05 mL/kg body weight (0.0227 mL/lb) which provides 0.17 mg moxidectin/kg body weight (0.0773 mg/lb). To ensure accurate dosing, calculate each dose based on the dog's weight at the time of treatment. Do not overdose growing puppies in anticipation of their expected adult weight. A dosage chart is included in the labeling to aid in determining the correct dose volume to be administered based on the dog's weight.

IV. Effectiveness

A. Dosage Characterization

Two dose determination studies were conducted to determine and confirm the dose of a single injection of the final ProHeart 6 formulation required to effectively prevent *Dirofilaria immitis* infections for a six-month period.

1. Study Number 0899-C-US-1-96

Title: Prophylactic Activity of Moxidectin-SR Injectable Formulation Against *Dirofilaria immitis* Infections in Beagles

Type of Study: Laboratory study

Purpose: The purpose of this study was to determine the minimum effective dose of ProHeart 6 needed to prevent canine heartworm infections for a six-month period.

Clinical Investigator: John McCall, Ph.D.
TRS Laboratories, Inc.
Athens, GA 30604

Animals: A total of 32 heartworm-negative, purpose-bred beagles (12 males and 20 females) approximately 9 to 24 months of age and weighing between 7.80 to 12.25 kg at the time of treatment were used in this study.

Dosage Groups (8 dogs per group):

Saline-treated controls
0.06 mg ProHeart 6/kg bodyweight (low-dose)
0.17 mg ProHeart 6/kg bodyweight (mid-dose)
0.50 mg ProHeart 6/kg bodyweight (high-dose)

Route of Administration: Subcutaneous injection in the dorsum of the neck

Test Duration: 327 days (treatment to necropsy).

Study Design: All dogs were determined to be negative for *D. immitis* by antigen test and modified Knott's test prior to study initiation. The dogs were treated on Day 0. At Day 180 (6 months) following treatment, all dogs were inoculated with 50 *Dirofilaria immitis* L₃ infective larvae. Infections were allowed to develop for 150 days (approximately 5 months) at which time each animal was euthanized and necropsied to determine the presence of heartworms. Following treatment, dogs were observed at approximately hourly intervals for six hours for adverse reactions to treatment and then twice daily for the next seven days. Injection sites were observed daily for the first 14 days posttreatment, weekly through Day 42 and then biweekly until the end of the study. Injection sites were also observed at necropsy and examined histologically. General health observations were made daily throughout the study. At necropsy, the heart and lungs of each test dog were removed for heartworm recovery and quantification.

Results: An average of 25 adult *D. immitis* was recovered from dogs in the control group. No worms were recovered from any of the dogs that received treatment with any level of ProHeart 6.

Conclusion: A single subcutaneous injection of ProHeart 6 for dogs was effective (100%) in preventing canine heartworm disease for six months at all tested dose levels.

Adverse Reactions: From Days 0-12, injection site reactions were noted in all four groups. The injection sites were readily visible and palpable and maintained either a soft or firm consistency. These findings continued until Day 14 in the control group. The injection sites remained visible and palpable in the mid-dose group on Days 13, 84, and 112 and in the high-dose group for the entire study duration. Additional observations are noted in the table below.

Table 1: Additional Injection Site Reactions

Day(s)	Observations
6	1 high-dose dog: 4-5 cm swelling, abscessed, draining reddish fluid
13, 14, 21	1 control dog: redness, exudate
21	1 control, 1 mid-dose, and 2 high-dose dogs: redness, exudate, and discoloration

Granulomas were observed during the histopathological examination of injection site tissues from dogs in all groups (1/8 in the control group, 4/8 in the low-dose group, 2/8 in the mid-dose group and 7/8 in the high-dose group). Overall, the granulomas were well defined and appeared to represent resolution/resorption of foreign material at the injection site.

2. Study Number 0899-C-US-2-96

Title: Prophylactic Activity of Moxidectin-SR Injectable Formulation Against *Dirofilaria immitis* Infections in Mongrel Dogs

Type of Study: Laboratory study

Purpose: The purpose of this study was to determine the minimum effective dose of ProHeart 6 needed to prevent canine heartworm infections for a six-month period.

Clinical Investigator: James B. Lok, Ph.D.
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, PA 19104

Animals: A total of 32 heartworm-negative, purpose-bred mongrel dogs (16 males and 16 females) at least 8 months of age and weighing between 10.8 to 21.5 kg at the time of treatment were used in this study.

Dosage Groups (8 dogs per group):
Saline-treated controls
0.06 mg ProHeart 6/kg bodyweight (low-dose)
0.17 mg ProHeart 6/kg bodyweight (mid-dose)
0.50 mg ProHeart 6/kg bodyweight (high-dose)

Route of Administration: Subcutaneous injection on the left side of the neck cranial to the scapula.

Test Duration: 331 days (treatment to necropsy).

Study Design: All dogs were determined to be negative for *D. immitis* by antigen test and modified Knott's test prior to initiation of the study. All dogs were treated on Day 0. At Day 180 (6 months) following treatment, all dogs were inoculated with 50 *Dirofilaria immitis* L₃ infective larvae. Infections were allowed to develop for 150 days (approximately 5 months) at which time each animal was euthanized and necropsied to determine the presence of heartworms. Following treatment, dogs were observed at approximately hourly intervals for six hours for adverse reactions to treatment and then twice daily for the next seven days. Injection sites were observed daily for the first 14 days posttreatment, weekly through Day 42 and then biweekly until the end of the study. Injection sites were also observed at necropsy and examined histologically. The heart and lungs of each test dog were removed at necropsy for heartworm recovery and quantification.

Results: An average of 36 adult *D. immitis* was recovered from dogs in the control group. At necropsy, no worms were recovered from any of the dogs in the high- or mid-dose groups. However, 14 adult *D. immitis* (4 males, 7 females and 3 head fragments) were found in one dog in the low-dose group (0.06 mg moxidectin/kg body weight).

Conclusion: A single subcutaneous injection of ProHeart 6 containing 0.17 mg moxidectin/kg bodyweight was the lowest dose level tested which prevented canine heartworm disease for a period of six months with 100% effectiveness.

Adverse Reactions: From Days 0-13, injection site reactions were noted in all groups. The injection sites were readily visible and palpable and maintained either a soft or firm consistency. Other observations, which appeared in all groups, are described in Table 2 below. The injection sites continued to be visible in the control groups up to Day 21 and palpable on Day 140 in the mid-dose group. The reactions continued through the remainder of the study in the high-dose group.

Table 2: Additional Injection Site Reactions in All Groups

Day(s)	Observations
0	Reddish patches, wheals at injection site
1	Pale reddish spots, bumps, patches
2	Pinkish focal spots, scabs at injection site
3-5	Small lumps, subcutaneous swelling, scabs at injection site
6-13	Lumps (nodules), pale brown scabs at injection sites

Histopathology revealed thirteen dogs in the low- (3), mid- (4), and high-dose (6) groups with granulomatous lesions of the panniculus muscle associated with moxidectin administration.

B. Dosage Confirmation – Hookworms

The effectiveness of a single subcutaneous injection of ProHeart 6 at the recommended dosage of 0.17 mg moxidectin/kg bodyweight against gastrointestinal nematodes present at the time of treatment was tested in three dose confirmation studies.

1. Study Number 0899-C-US-12-98

Title: Efficacy of Moxidectin Canine SR Injectable against Nematodes

Type of Study: Laboratory study with natural infections

Purpose: The purpose of this study was to evaluate the effectiveness of the recommended 0.17 mg moxidectin/kg bodyweight dosage of ProHeart 6 versus natural infections of roundworms (*Toxocara canis* and/or *Toxascaris leonina*) and hookworms (*Ancylostoma caninum* and/or *Uncinaria stenocephala*).

Clinical Investigator: Robyn L. Stone
Professional Laboratory & Research Services, Inc.
Corapeake, NC 27926

Animals: A total of 22 mixed-breed and purebred dogs (7 males and 15 females) weighing between 1.20 to 15.10 kg and naturally infected with both roundworms and hookworms at the time of treatment were used in this study.

Dosage Groups (11 dogs per group):

Saline-treated control

0.17 mg ProHeart 6/kg bodyweight

Route of Administration: Subcutaneous injection on the left side of the neck.

Study Duration: 17 days (treatment to necropsy).

Study Design: All dogs were confirmed positive for nematode infections by fecal egg-per-gram (EPG) counts prior to initiation of the study. The dogs were observed at approximately 3, 6 and 24 hours posttreatment and then once daily until necropsy for general health and signs of any adverse reaction to treatment. Injection sites were observed once daily from treatment until necropsy. Dogs were sacrificed and their gastrointestinal tracts processed for nematode recovery and quantification.

Results: Based on the worm counts of control dogs at necropsy, only the *Ancylostoma caninum* and *Toxocara canis* infections were adequate for evaluation. For each of these parasite species, effectiveness was calculated as follows:

Table 3: Effectiveness Against *A. caninum* and *T. canis*

Parasite	Treatment	Geometric Mean	% Effectiveness
<i>Ancylostoma caninum</i>	Control	17.17	
	Moxidectin	00.13	99.22%
<i>Toxocara canis</i>	Control	19.41	
	Moxidectin	36.93	<0.00%

Conclusion: A single subcutaneous injection of ProHeart 6 given at the recommended dosage of 0.17 mg moxidectin/kg bodyweight was $\geq 90\%$ effective against natural infections of *Ancylostoma caninum*.

Adverse Reactions: No adverse reactions to treatment were reported in any of the test dogs. No injection site abnormalities were reported at any observation time.

2. Study Number 0899-C-US-15-99

Title: Efficacy of Moxidectin Canine SR Injectable against Experimental Hookworm Infections in Dogs in Georgia

Type of Study: Laboratory study with induced infections

Purpose: The purpose of this study was to evaluate the effectiveness of 0.17 mg moxidectin/kg bodyweight dosage of ProHeart 6 against experimental infections of the larval and adult stages of two canine hookworm species (*Ancylostoma caninum* and *Uncinaria stenocephala*).

Clinical Investigator: John McCall, Ph.D.
TRS Labs, Inc.
Athens, GA 30604

Animals: A total of 30 purpose-bred beagle dogs (15 males and 15 females) weighing between 8.90 to 16.30 kg at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Controls treated with saline solution on Day 6 and Day 28 post-infection.

0.17 mg ProHeart 6/kg bodyweight on Day 6 post-infection. Second treatment with saline solution on Day 28 post-infection.

0.17 mg ProHeart 6/kg bodyweight on Day 28 post-infection. Initial treatment with saline solution on Day 6 post-infection.

Route of Administration: Subcutaneous injection on the left side of the neck.

Study Duration: 42 days (experimental infection to necropsy).

Study Design: All dogs were determined to be free from helminth infections by fecal EPG prior to initiation of the experiment. Dogs were infected with 200 L₃ *A. caninum* on Day 0 and 400 L₃ *U. stenocephala* on Day 1. Following treatment on Day 6 and Day 28, dogs were observed at approximately 3, 6 and 24 hours posttreatment for any signs of adverse reactions. Observations for general health were made once daily on all other days. Dogs were sacrificed on Day 42 and their gastrointestinal tracts were processed for nematode recovery and quantification.

Results: Based on the worm counts of control dogs at necropsy, only the *Ancylostoma caninum* infections were adequate for evaluation. For *Ancylostoma caninum* infections, effectiveness was calculated as follows:

Table 4: Effectiveness Against *A. caninum*

Parasite	Treatment	Geometric Mean	% Effectiveness
<i>Ancylostoma caninum</i>	Control	58.91	
	Moxidectin – Day 6	0.0	100.0%
	Moxidectin – Day 28	0.0	100.0%

Conclusion: A single subcutaneous injection of ProHeart 6 for dogs given at the recommended dosage of 0.17 mg moxidectin/kg bodyweight was $\geq 90\%$ effective against larval and adult stages of *Ancylostoma caninum*.

Adverse Reactions: Two moxidectin treated animals had isolated occurrences of soft feces. No injection site abnormalities were reported at any observation time.

3. Study Number 0899-C-US-16-99

Title: Efficacy of Moxidectin Canine SR Injectable against Experimental Hookworm Infections in Dogs in Michigan

Type of Study: Laboratory study with induced infections

Purpose: The purpose of this study was to evaluate the effectiveness of the recommended 0.17 mg moxidectin/kg bodyweight dose rate of ProHeart 6 against experimental infections of the larval and adult stages of two canine hookworm species (*Ancylostoma caninum* and *Uncinaria stenocephala*).

Clinical Investigator: Dwight D. Bowman
Cornell University
Ithaca, NY 14853
(Test facility location: Stanwood, Michigan)

Animals: A total of 30 purpose-bred beagle dogs (15 males and 15 females) weighing between 6.92 to 12.54 kg at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Controls treated with saline solution on Day 6 and Day 28 post-infection.

0.17 mg ProHeart 6/kg bodyweight on Day 6 post-infection. Second treatment with saline solution on Day 28 post-infection.

0.17 mg ProHeart 6/kg bodyweight on Day 28 post-infection. Initial treatment with saline solution on Day 6 post-infection.

Route of Administration: Subcutaneous injection on the left side of the neck.

Study Duration: 42 days (experimental infection to necropsy).

Study Design: All dogs were determined to be free from hookworm infection by fecal EPG prior to initiation of the experiment. Dogs were infected with 200 L₃ *A. caninum* and 400 L₃ *U. stenocephala* on Day 0. Following treatment on Day 6 and Day 28, dogs were observed at approximately 3, 6 and 24 hours posttreatment for any signs of adverse reaction to treatment. Observations for general health were made once daily on all other days. Dogs were sacrificed on Day 42 and their gastrointestinal tracts were processed for nematode recovery and quantification.

Results: Based on the worm counts of control dogs at necropsy, both the *Ancylostoma caninum* and *Uncinaria stenocephala* infections were adequate for evaluation.

Table 5: Effectiveness Against *A. caninum* and *U. stenocephala*

Parasite	Treatment	Geometric Mean	% Effectiveness
<i>Ancylostoma caninum</i>	Control	48.6	
	Moxidectin – Day 6	0.0	100.0%
	Moxidectin – Day 28	0.0	100.0%
<i>Uncinaria stenocephala</i>	Control	28.5	
	Moxidectin – Day 6	0.0	100.0%
	Moxidectin – Day 28	0.0	100.0%

Conclusion: A single subcutaneous injection of ProHeart 6 for dogs given at the recommended dosage of 0.17 mg moxidectin/kg bodyweight was $\geq 90\%$ effective in the treatment of larval and adult stages of *Ancylostoma caninum* and *Uncinaria stenocephala*.

Adverse Reactions: No adverse reactions to treatment were reported. No injection site abnormalities were reported at any observation time.

C. Clinical Field Study

Title: Safety and Efficacy of Moxidectin Canine SR Injectable for Prevention of Heartworm Disease in Dogs under Conditions of Field Use

Type of Study: Clinical field study

Purpose: The purpose of this study was to evaluate the safety and effectiveness of the recommended 0.17 mg moxidectin/kg body weight dosage of ProHeart 6 for dogs given at six-month intervals under field conditions.

Participating Clinics and Primary Clinicians:

Dr. Chris Hesse
Golden Lantern Animal Hospital
Dana Point, CA 92641

Dr. Richard Heers
Cross Street Veterinary Clinic
Tulare, CA 93274

Dr. Wick Culp
Animal Medical Center
Amarillo, TX 79106

Dr. David Hodges
Coulter Animal Hospital
Amarillo, TX 79120

Dr. K. C. Brooks
Lodi Veterinary Hospital
Lodi, WI 53555

Dr. William Gengler
Animal Hospital of Verona
Verona, WI 53593

Dr. Steven Levy
Durham Veterinary Hospital
Durham, CT 06422

Animals: A total of 374 client-owned dogs (280 treated, 94 control) of various breeds from six months to 15 years of age completed this study.

Dosage Groups:

Control group: ProHeart[®] (moxidectin) Tablets administered every 30 days at the approved minimum dose of 3 μg moxidectin/kg bodyweight.

Treated group: ProHeart 6 at Month 0 and Month 6 at the recommended dose of 0.17 mg moxidectin/kg bodyweight.

Route of Administration:

Control group: Oral

Treated group: Subcutaneous injection in the dorsal neck cranial to the scapula.

Test Duration: Approximately 365 days.

Study Design: Prior to enrollment and at Month 3, all animals were tested for both heartworm antigen with the IDEXX Snap Heartworm Antigen Test and circulating microfilaria using the microfilarial filtration (Knott's) test to ensure the absence of existing dirofilariasis. At 6 and 12 months after treatment initiation the following were performed: antigen and microfilaria tests, physical exams and injection site evaluations.

Results: None of the 374 dogs that completed this study tested positive for heartworms at either the 3-, 6- or 12-month checks.

Conclusion: Under field conditions, a single subcutaneous injection of ProHeart 6 for dogs given at the recommended dosage of 0.17 mg moxidectin/kg body weight was safe and effective in protecting a wide variety (in terms of age, sex and breed) of dogs against heartworm infection for a six-month period.

Adverse Reactions: The following potential adverse drug reactions (number of cases) were observed in the moxidectin injectable treatment group: vomiting (3), diarrhea (2), weight loss (2), listlessness (1), seizures (1), injection site pruritus (3), elevated body temperature (1). Injection site evaluations of the ProHeart 6 treated dogs revealed no abnormalities.

Two geriatric dogs with a history of weight loss after the initial ProHeart 6 injection died within a month of the second 6-month injection. A third dog who was underweight for its age and breed and who had a history of congenital problems experienced lethargy following the initial injection of ProHeart 6. The dog never recovered and died 3 months later. Treatment with ProHeart 6 could not be ruled out as contributing to these observations.

V. Animal Safety

A. Target Animal Toxicity Study -- Study No. 0899-C-US-4-98

Title: Three Month Target Animal Safety Study (Toxicity) with Moxidectin Canine SR Injectable Formulation

Type of Study: Laboratory safety study

Investigator: Peter J. Thomford, Ph.D.
Covance Laboratories, Inc.
Madison, Wisconsin 53704

Purpose: The objective of this study was to evaluate the clinical and pathological effects when the final ProHeart 6 formulation was administered to healthy dogs at either 1X, 3X or 5X the recommended dose rate of 0.17 mg moxidectin/kg body weight.

Animals: Thirty-two purpose-bred beagles (16 males and 16 females) approximately 7 to 8 months of age at the time of treatment were used in this study. The males weighed from 8.6 to 13.5 kg and the females weighed 7.8 to 12.0 kg at the time of treatment.

Control: Sodium Chloride for Injection, USP 0.9%.

Dosage Form: ProHeart 6 microspheres constituted with ProHeart 6 vehicle.

Route of Administration: Subcutaneous injection in the cervical region (left and/or right side of the neck). No more than 2.0 mL was injected in a single site.

Dosage Groups (8 dogs per group):

Controls treated with saline solution.

0.17 mg moxidectin/kg body weight (recommended dose level).

0.51 mg moxidectin/kg body weight (3X recommended dose level).

0.85 mg moxidectin/kg body weight (5X recommended dose level).

Study Duration: Three months.

Pertinent Measurements/Observations: Physical examinations were conducted prior to treatment and during Weeks 2, 6, and 10 post treatment. Venous blood samples and urine were collected for hematology, clinical chemistry, coagulation, and urinalysis once pretreatment (Week -2) and during Weeks 4, 8, and 13 after treatment. Test animals were observed for clinical signs once hourly for the first four hours following treatment and then at 6, 8, 12, and 24 hours post treatment. For the remainder of the study the test animals were observed twice daily for mortality and morbidity. Food consumption and body weights were recorded prior to treatment, on the day of treatment, and then weekly throughout the remainder of the study. Test animals were sacrificed and necropsied three months after treatment. All animals were evaluated for gross pathology. Tissues were collected from all animals. Tissues from the control and high-dose (5X) treatment groups were examined microscopically.

Results:

1. Clinical Observations:

(a) Injection sites

Swelling or slight edema was observed in the moxidectin-treated groups in the first 3 weeks of the study, as described in the following table.

Table 6: Injection Site Reactions

	Control	Moxidectin Treatment Group		
		1X	3X	5X
Incidence	0/8	3/8	5/8	3/8
Days observed ¹	-	8 – 20	1 ² - 19	1 ³ - 19

¹ First day observed in any affected dog – Last day observed in any affected dog.

² First noticed at 8 hours post treatment

³ First noticed at 12 hours post treatment

(b) One 5X female displayed excessive salivation on Day 78.

- 2. Feed Consumption:** There were no statistically significant differences between treatment groups.
- 3. Body Weight:** There were no statistically significant differences between treatment groups.
- 4. Hematology, Coagulation, Serum Chemistry:** A comparison of pre- and post treatment hematology, coagulation, and clinical chemistry values indicated no clinically significant changes.
- 5. Urinalysis:** There were no statistically significant differences between treatment groups.
- 6. Pathology Observations:** The only gross lesion associated with the test article was a 2.0 cm red foci at the injection site in one 5X male. Microscopic evaluation of all major organ tissues obtained from test animals in the high dose (5X) group at necropsy, including the injection sites, revealed no histopathologic changes indicative of a toxic effect.

Conclusion: A single subcutaneous injection of the final ProHeart 6 formulation equivalent to either 1X, 3X or 5X the recommended dose level caused swelling/slight edema at the site of injection starting within 8 hours of injection and lasting for up to 3 weeks. One dog at the 5X dose displayed excessive salivation at Day 78 post treatment.

B. Safety in Dogs with Heartworm Infections -- Study No. 0899-C-US-14-98

Title: Clinical Observations from the Administration of Moxidectin Canine Sustained Release Injectable in Heartworm Positive Dogs

Type of Study: Laboratory safety study

Investigator: Byron L. Blagburn, Ph.D.
Auburn University
Auburn, Alabama 36830

Purpose: The objective of this study was to evaluate the effect of treatment of heartworm-positive dogs with the final ProHeart 6 formulation.

Animals: Twenty heartworm-positive dogs (eleven males and nine females) of various breeds and mixes, weighing between 14 and 32 kg at the time treatment.

Control: The control animals were not treated.

Dosage Form: ProHeart 6 microspheres constituted with ProHeart 6 vehicle.

Route of Administration: Subcutaneous injection between the shoulder blades. The dose was split into two approximately equal sites.

Dosage Groups (10 dogs per group):

Untreated controls

0.51 mg moxidectin/kg body weight (3X recommended dose level).

Study Duration: 28 days.

Pertinent Measurements/Observations: Dogs were confirmed to be heartworm positive prior to study by both antigen testing and by microscopic analysis for microfilaria in blood smears. Health observations were made at 2, 4, 8, and 12 hours following treatment. Physical examinations were carried out prior to treatment, and on Days 14 and 27 post treatment. Microfilarial counts were conducted weekly. The test animals were evaluated for the presence of adult heartworms at necropsy.

Results: Adult heartworm counts at necropsy and microfilaria counts in blood demonstrated that all dogs had patent heartworm infections on Day 0 and throughout the study. No drug-related effects were noted in any of the dogs post treatment. Microfilaria counts in the moxidectin-treated group decreased from Day 7 to the end of the study.

Conclusion: A single subcutaneous injection of the final ProHeart 6 formulation equivalent to 3X the recommended dose level did not produce any adverse clinical or gross pathological effects in dogs infected with patent infections of heartworm.

C. Safety in Ivermectin-Sensitive Dogs -- Study No. 0899-C-US-13-98

Title: Clinical Observations from the Administration of Moxidectin Canine Sustained Release Injectable to Ivermectin-Sensitive Dogs

Type of Study: Laboratory safety study

Investigator: Alan J. Paul, D.V.M.
University of Illinois
Urbana, Illinois 61802

Purpose: The objective of this study was to evaluate the effect of treatment of collie dogs with demonstrated sensitivity to ivermectin with 1X, 3X and 5X levels of the final ProHeart 6 formulation.

Animals: Fifteen ivermectin-sensitive collies (10 males and 5 females), between 8 and 78 months of age and 19 – 29 kg body weight at time of moxidectin treatment, participated in this study. These animals were selected on the basis of having previously exhibited clinical signs of ivermectin toxicosis including depression, ataxia, mydriasis and excessive salivation.

Control: Results were compared to the well-documented, historical effects of avermectins in dogs of the sensitive breed.

Dosage Form: ProHeart 6 microspheres constituted with ProHeart 6 vehicle.

Route of Administration: Subcutaneous injection in the lateral aspect of the neck. No more than 3.0 mL was injected per location.

Dosage Groups (5 dogs per group):

0.17 mg moxidectin/kg body weight (recommended dose level).

0.51 mg moxidectin/kg body weight (3X recommended dose level).

0.85 mg moxidectin/kg body weight (5X recommended dose level).

Study Duration: 20 days.

Pertinent Measurements/Observations: Health observations were made at 1, 2, 3, 4, 5, 6, 7, 8, 12 and 18 hours after treatment, and then twice daily for 20 days.

Results: No adverse reactions were observed in any of the treated dogs.

Conclusion: A single subcutaneous injection of the final ProHeart 6 formulation equivalent to either 1X, 3X or 5X the recommended dose level did not produce any adverse reactions in collie dogs with demonstrated sensitivity to ivermectin.

D. Female Reproductive Safety -- Study No. 0899-C-US-3-98

Title: A Reproductive Study of Moxidectin Canine SR Injectable in Female Beagle Dogs Following Subcutaneous Injection

Type of Study: Laboratory safety study

Investigator: Larry H. Hulsebos, D.V.M.
MPI Research
Mattawan, Michigan 49071

Purpose: The objective of this study was to assess the effects of the treatment of female dogs with 3X levels of the final ProHeart 6 formulation at either one month prior to mating, at mating, during gestation, or shortly after whelping.

Animals: Forty purpose-bred adult female beagles with a history of successful breeding performance were included in the study. Twenty-five untreated males were used in the breeding phase of the trial.

Control: Untreated controls.

Dosage Form: ProHeart 6 microspheres constituted with ProHeart 6 vehicle.

Route of Administration: Subcutaneous injection in the lateral aspects of the neck (right and/or left sides). No more than 2.0 mL was injected in a single site.

Dosage Groups (8 female dogs per group): All treated test dogs received a single injection containing 3X the recommended dose rate (0.51 mg moxidectin/kg body weight). The timing of the treatments varied between groups in order to cover all critical periods of the reproductive cycle.

Untreated control

Pre-mating (approximately one month prior to mating).

The day after mating.

Day 28 of gestation period.

The fifth day after whelping.

Study Duration: Each female dog remained under observation until her puppies were weaned at six weeks of age.

Pertinent Measurements/Observations: Adults were given a complete physical exam prior to study initiation. Following treatment, test dogs were weighed and subjected to detailed clinical exams weekly throughout the remainder of the study period. Puppies were observed twice daily (cageside) for survival and obvious changes in appearance and behavior. Individual body weight measurements were taken and detailed physical examinations were performed when the puppies were 1, 4, 7, 14, 21, 28, 35, and 42 days old. A complete post mortem examination was performed on each puppy that died during the observation period.

Results: All eight females in each group were successfully mated, with no evidence of treatment-related breeding problems. Table 7 shows the major reproductive parameters measured.

Table 7: Reproductive Parameters

Treatment Group	Number with Litters (%)	Mean Gestation Period (days)	Total pups per litter	Live pups per litter
Untreated Control	7/8 (87.5 %)	64.9	5.3	5.3
Pre-mating	7/8 (87.5 %)	64.9	6.6	6.3
Mating	7/8 (87.5 %)	66.4	5.6	5.6
Day 28 of gestation	8/8 (100%)	65.6	5.5	5.3
Day 5 post-whelping	7/8 (87.5 %)	63.6	6.4	6.3

Conclusion: No adverse effects in terms of conception, pregnancy maintenance, and the development, growth and health of the puppies were seen when female dogs were treated with a single 3X level injection of the final ProHeart 6 formulation at critical times throughout their reproductive cycles (pre-mating through post-whelping).

E. Male Reproductive Safety -- Study No. 0899-C-CN-01-98

Title: Effects of Moxidectin Canine Sustained Release Injectable Solution on the Seminal Quality of Breeding Beagles

Type of Study: Laboratory safety study

Investigator: Dr. Donal McKeown
 International Bio-Institute Corp. (IBI)
 Fergus, Ontario, Canada N1M 2W4

Purpose: The objective of this study was to assess the effects of the treatment of male dogs with 3X levels of the final ProHeart 6 formulation on semen quality.

Animals: Sixteen healthy, sexually-mature, male beagle dogs between 29 and 73 months of age and 11 – 17 kg body weight were used in this study.

Control: Sodium chloride for Injection, USP 0.9%.

Dosage Form: ProHeart 6 microspheres constituted with ProHeart 6 vehicle.

Route of Administration: Subcutaneous injection in the dorsum of the neck anterior to the scapula.

Dosage Groups (8 dogs per group):

Controls treated with saline solution.

0.51 mg moxidectin/kg body weight (3X the recommended dose rate).

Study Duration: 91 days.

Pertinent Measurements/Observations: The semen quality of each dog was determined on ejaculates taken two times pretreatment (Day -21 and Day -7), and seven times post treatment on Days 7, 21, 35, 42, 63, 77, and 91. Animals were observed for adverse reactions at least once a day during the study. The dogs received complete physical exams prior to treatment on Day -21, the day of treatment and Days 35 and 91 post treatment.

Results: No clinically significant changes/abnormalities were noted in semen quality (motility, morphology, volume and concentration). Injection site reactions were noted in 5/8 control animals and 6/8 treated animals. Reactions seen included redness, swelling and subcutaneous lumps and nodules. All injection site reactions resolved by Day 17.

Conclusion: A single subcutaneous injection of the final ProHeart 6 formulation administered to male dogs at three times the recommended dose rate did not have an adverse effect on semen quality. Injection site reactions were noted in the control and treated dogs for the first 3 weeks of the study.

F. Repeated Treatment Safety -- Study No. 0899-C-US-9-98

Title: Three-Year Study with Moxidectin Canine SR Injectable

Type of Study: Laboratory safety study

Investigator: William Barton, Ph.D.
CAVL
Amarillo, Texas 79118

Purpose: The objectives of this study were 1) to determine the effects at the injection site of multiple 1X treatments of final ProHeart 6 formulation administered at six-month intervals and 2) to assess the level of drug exposure following multiple administrations at the recommended dosing interval.

Animals: Sixteen male beagle dogs between 9 and 20 months of age at the time of the first treatment were used in this study.

Control: ProHeart® (moxidectin) Tablets

Dosage Form: ProHeart 6 microspheres constituted with ProHeart 6 vehicle.

Dosage Groups (4 dogs per group):

ProHeart (moxidectin) Tablets orally every month

1 year group - 0.17 mg moxidectin/kg body weight every 6 months for 2 injections

2 year group - 0.17 mg moxidectin/kg body weight every 6 months for 4 injections

3 year group - 0.17 mg moxidectin/kg body weight every 6 months for 6 injections

Two dogs in each group treated with moxidectin injectable were injected on the right side of the neck at each treatment and the other two dogs were injected on alternating sides of the neck at each treatment.

Study Duration: 927 days.

Pertinent Measurements/Observations: All dogs were observed daily for adverse reactions throughout the study. Injection sites were monitored prior to each treatment and at 1, 3, 7 and 14 days following each treatment. Four test dogs were sacrificed at the end of the first and second years of the study. Injection site tissues taken at necropsy from these eight dogs were examined for gross and microscopic pathology. Dogs in the “3 year group” were not sacrificed. A series of blood samples were taken for moxidectin serum concentration analysis in conjunction with the first and sixth treatment periods.

Results:

- 1. Clinical Observations:** One dog had a 1.8 kg weight loss in the six months between the first injection and the second injections. The dog showed no other clinical signs. One other dog had a slight swelling at the injection site on Day 1 of the study.
- 2. Pathology Observations:** Mild erythema and localized deep subcuticular thickening were seen grossly in the dogs that received four injections in the same anatomical area and in 1 dog that received two injections in the same area. Microscopic evaluation of the injection site tissues from all treated dogs consistently showed mild granulomatous panniculitis with microvacuolation thought to be caused by the microsphere component of the drug.
- 3. Moxidectin Serum Levels:** The following table shows the mean moxidectin serum levels after the first injection.

Table 8: Mean Moxidectin Serum Levels (ppb) from Day -1 to Day 28

-1	1	3	5	7	10	14	21	28
<0.5	1.30	3.34	4.76	5.12	5.06	4.52	3.56	3.11

Following injection with the 1X dose of ProHeart 6, peak moxidectin blood levels were observed approximately 7 – 14 days after treatment. By Day 112 after the first treatment, moxidectin serum levels were below the limit of quantification (0.5 ppb) in 10 of the 12 treated dogs. Measurements taken prior to the fifth and sixth injections showed consistently low moxidectin serum levels. Accordingly, little or no drug accumulation occurred with repeated administrations.

Conclusion: Subcutaneous injections of 1X doses of final ProHeart 6 formulation administered up to six times at six-month intervals did not result in significant injection site pathology. However, repeated injections in the same location may cause thickening at that site. Little or no drug accumulation is expected to occur with repeated administrations.

VI. Human Safety

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

Human Warnings are provided on the product label as follows:

“Not for human use. Keep this and all drugs out of the reach of children. May be slightly irritating to the eyes. May cause slight irritation to the upper respiratory tract if inhaled. May be harmful if swallowed. If contact with the eyes occurs, rinse thoroughly with water for 15 minutes and seek medical attention immediately. If accidental ingestion occurs, contact a Poison Control Center or a physician immediately. The material safety data sheet (MSDS) contains more detailed occupational safety information.”

VII. Agency Conclusions

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that ProHeart 6 (moxidectin) Sustained Release Injectable for Dogs, when used under labeled conditions of use, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of heartworm infections, to monitor the safe use of the product and to administer the injectable product.

Under section 512(c)(2)(F)(ii) of the FFDCFA, 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 or any studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

Fort Dodge holds Patent No. 4916154 for moxidectin which expires on April 10, 2007.

VIII. Labeling (Attached)

- A. Package Insert
- B. Vials (microspheres and vehicle)
- C. Box