Approval Date: June 13, 2002

FREEDOM OF INFORMATION SUMMARY

Supplemental NADA 141-189

ProHeart® 6 (moxidectin) Sustained Release Injectable for Dogs

Additional indication for the treatment of existing larval and adult hookworm (*Uncinaria stenocephala*) infections

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.

Effect of Supplement: New indication for the treatment of existing larval and adult hookworm (*Uncinaria stenocephala*) infections.

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 and Uncinaria stenocephala*) 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

An original new animal drug application for ProHeart 6 (moxidectin) Sustained Release Injectable for Dogs (NADA 141-189) was approved on June 6, 2001 (66 FR 35756, July 9, 2001). All aspects of this NADA 141-189 drug approval are codified in 21 CFR 522.1451. The supporting studies demonstrating the effectiveness of ProHeart 6 against all parasites listed in the originally approved labeling when administered at the recommended 0.17 mg moxidectin/kg body weight dose level are summarized in the original June 6, 2001 NADA 141-189 Freedom of Information Summary. This NADA 141-189 supplement provides additional effectiveness data confirming the efficacy of a single administration of ProHeart 6 at the currently approved 0.17 mg/kg body weight dose rate against existing infections of larval and adult *Uncinaria stenocephala.* The approval of these new indications for the treatment of existing larval and adult *Uncinaria stenocephala* infections is supported by data from four effectiveness studies. Summaries of the relevant aspects of these four studies are presented below.

Dose Confirmation – Hookworms (*Uncinaria stenocephala*)

The effectiveness of a single subcutaneous injection of ProHeart 6 at the recommended 0.17 mg moxidectin/kg bodyweight dose rate against larval and adult *Uncinaria stenocephala* infections present at the time of treatment was evaluated in four dose confirmation studies.

1. 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 moxidectin/kg bodyweight on Day 6 post-infection. Second treatment with saline solution on Day 28 post-infection.

0.17 mg moxidectin/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 Eggs Per Gram (EPG) prior to initiation of the experiment. Dogs were infected with 200 L_3 *A. caninum* and 400 L_3 *U. stenocephala* on Day 0. Following treatment on Day 6 and Day 28, dogs were observed at approximately 3, 6 and 24 hours post-treatment for any signs of adverse reaction to treatment. Observations for general health were made once daily on all other days. The Day 6 and Day 28 treatments were designed to furnish data pertaining to the efficacy of the drug against the larval/immature and adult stages (respectively) of these two canine hookworm species. 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 2: Effectiveness Against *Uncinaria stenocephala*

Parasite	Treatment	Geometric Mean	% Effectiveness
U. stenocephala	Control	28.5	
	Moxidectin – Day 6	0.0	100.0% (larvae)
	Moxidectin – Day 28	0.0	100.0% (adults)

Conclusion: A single subcutaneous injection of ProHeart 6 given at the recommended dose level of 0.17 mg moxidectin/kg bodyweight was ≥ 90% effective in the treatment of larval and adult stages of *Uncinaria stenocephala.*

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

2. Study Number 0899-C-US-17-99

Title: Efficacy of Moxidectin Canine SR Injectable against Experimental Infections of Hookworms and Whipworms 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 the canine whipworm (*Trichuris vulpis*) and 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 40 purpose-bred beagle dogs (20 males and 20 females) weighing between 8.82 to 16.80 kg at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Two controls groups administered saline solution on Days 42 or 91 post-infection.

Two groups given 0.17 mg moxidectin/kg bodyweight on Days 42 or 91 post-infection with *T. vulpis.*

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

Study Duration: 49 and 105 days (from experimental infection with *T. vulpis* to necropsy).

Study Design: All dogs were determined to be free from hookworm and whipworm infections by fecal EPG prior to initiation of the experiment All dogs were infected with 500 embryonated *T. vulpis* eggs on Day 0. All dogs were subsequently infected with 200 L_3 *A. caninum* on Day 36 and dogs from only one treated and one control group were infected with 200 L_3 *U. stenocephala* on Days 37. The dogs in the two groups infected with *T. vulpis*, *A. caninum* and *U. stenocephala* were treated approximately a week later on Day 42. hese two groups of dogs were sacrificed seven days after treatment on Day 49 and their gastrointestinal tracts were processed for nematode recovery and quantification. The remaining two groups of *A. caninum* and *T. vulpis*-infected dogs were treated on Day 91 and sacrificed 14 days later on Day 105 for nematode recovery and quantification. All dogs were observed at approximately 3, 6 and 24 hours post-treatment for any signs of adverse reaction to treatment. Observations for general health were made once daily on all other days.

Results: Based on the worm counts of control dogs at necropsy, only the *Ancylostoma caninum* and *Uncinaria stenocephala* infections were adequate for evaluation. The effectiveness calculated from the comparison of the group of *Uncinaria stenocephala*-infected treated with ProHeart 6 and the associated control group in this study is shown below.

Table 3: Effectiveness Against *Uncinaria stenocephala* Larvae

Parasite	Treatment	Geometric Mean	% Effectiveness
U. stenocephala larvae	Control	13.64	
	Moxidectin	0.0	99.5%

Conclusion: A single subcutaneous injection of ProHeart 6 given at the recommended dosage of 0.17 mg moxidectin/kg bodyweight was ≥ 90% effective in the treatment of larval stages of *Uncinaria stenocephala.*

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

3. Study Number 0899-C-US-18-99

Title: Efficacy of Moxidectin Canine SR Injectable against Larval/Immature Stages of Experimental *Trichuris vulpis* (Whipworms), *Ancylostoma caninum* and *Uncinaria stenocephala* (Hookworms) Infections in Dogs in New Jersey

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 the canine whipworm (*Trichuris vulpis*) and the larval stages of two canine hookworm species (*Ancylostoma caninum* and *Uncinaria stenocephala*).

Clinical Investigator: Sivaja Ranjan
Fort Dodge Animal Health
Princeton, NJ 08543
(Test facility location: Monmouth Junction New Jersey)

Animals: A total of 36 purpose-bred beagle dogs (18 males and 18 females) weighing between 8.20 to 11.85 kg at the time of treatment were used in this study.

Dosage Groups (9 dogs per group):

Two control groups administered saline solution on Day 42 post-infection with *T. vulpis* (five and six days post-infection with *U. stenocephala* and *A. caninum*, respectively).

Two groups treated with 0.17 mg moxidectin/kg bodyweight on Day 42 post-infection with *T. vulpis* (five and six days post-infection with *U. stenocephala* and *A. caninum*, respectively).

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

Study Duration: 49 and 56 days (from experimental infection with *T. vulpis* to necropsy).

Study Design: All dogs were determined to be free from hookworm and whipworm infections by fecal EPG prior to initiation of the experiment. Dogs were infected with 500 embryonated *T. vulpis* eggs on Day 0. Dogs were subsequently infected with 200 L_3 *A. caninum* on Day 36 and 200 L_3 *U. stenocephala* on Days 37. All groups were treated on Day 42 when all nematodes were in larval or immature stages of development. Following treatment on Day 42, dogs were observed at approximately 3, 6 and 24 hours post-treatment for any signs of adverse reaction to treatment. Observations for general health were made once daily on all other days. One group of treated and one group of control dogs were sacrificed on Day 49 (seven days post-treatment) and their gastrointestinal tracts were processed for nematode recovery and quantification. The remaining groups of treated and control dogs were sacrificed on Day 56 (14 days post-treatment) and identically processed for nematode recovery and quantification.

Results: Based on the worm counts of control dogs at necropsy only the *Ancylostoma caninum* and *Uncinaria stenocephala* infections were adequate for evaluation. The effectiveness calculations for the two *Uncinaria stenocephala* larval infections evaluated in this study are presented below.

Table 4: Effectiveness Against *Uncinaria stenocephala* Larvae

Parasite	Treatment	Geometric Mean	% Effectiveness
U. stenocephala larvae (7 days posttreatment)	Control	21.0	
	Moxidectin	0.2	99.0%
U. stenocephala larvae (14 days posttreatment)	Control	45.4	
	Moxidectin	0.0	100%

Conclusion: A single subcutaneous injection of ProHeart 6 given at the recommended dosage of 0.17 mg moxidectin/kg bodyweight was ≥ 90% effective in the treatment of the larval stages of *Uncinaria stenocephala.*

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

4. Study Number 0899-C-US-19-99

Title: Efficacy of Moxidectin Canine SR Injectable against Experimental Infections of *Uncinaria stenocephala* in Dogs in Georgia

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 in dogs experimentally infected with *Uncinaria stenocephala*.

Clinical Investigator: John McCall, Ph.D.
TRS Labs, Inc.
Athens, GA 30605
(Test facility location: Athens, Georgia)

Animals: A total of 30 purpose-bred beagle dogs (6 males and 24 females) weighing between 7.15 to 13.30 kg were used in this study.

Dosage Groups (10 dogs per group):

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

0.17 mg moxidectin/kg bodyweight on Day 6 post-infection and saline solution on on Day 28 post-infection.

0.17 mg moxidectin/kg bodyweight on Day 28 post-infection and saline solution on Day 6 post-infection.

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

Study Duration: 42 days (from 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 400 L_3 *U. stenocephala* on Day 0. Following treatment on Day 6 and Day 28, dogs were observed at approximately 3, 6 and 24 hours post-treatment 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, *Uncinaria stenocephala* infections were adequate for evaluation. The percent efficacy reported in the dogs treated on Day 6 post-infection is indicative of effectiveness against larval stages of *U. stenocephala*. The percent efficacy reported in the dogs treated on Day 28 post-infection is indicative of efficacy against adult *U. stenocephala*. The effectiveness calculated for both larval and adult stage *U. stenocephala* infections in this study is shown in below.

Table 5: Efficacy Against *Uncinaria stenocephala*

Parasite	Treatment	Geometric Mean	% Effectiveness
U. stenocephala	Control	225.4	
	Moxidectin – Day 6	0.93	99.6% (larvae)
	Moxidectin – Day 28	1.24	99.5% (adults)

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

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

V. Animal Safety

The approval of this supplemental NADA 141-189 is for a new indication. It does not change the dose level, frequency or route of administration of ProHeart 6 (moxidectin) Sustained Release Injectable for Dogs or the class or species of treated animals. Consequently, no additional animal safety data were required for approval of this new indication.

VI. Human Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental 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 in the treatment of existing larval and adult infections of *Uncinaria stenocephala*.

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)(iii) 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 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