FORT DODGE
ANIMAL HEALTH

Revision: .... [illegible]
Operator: .... [illegible]
Date: .... [illegible]
Product ID#: 3670G
Reference #: .... [illegible]
Product Name: .... ProHeart 6
Type/Size: .... [illegible]
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Folded: .... [illegible]
File Path: .... [illegible]
PDF: .... [illegible]

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ProHeart® 6

ProHeart® 6

NADA 141-189, Approved by FDA

ProHeart® 6
(moxidectin)

Sustained Release Injectable for Dogs

CAUTION

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

[illegible]

PHARMACOLOGY

[illegible]

[illegible]

[illegible]

INDICATIONS

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.

DOSAGE AND ADMINISTRATION

Frequency of Treatment: [illegible]

[illegible]

Dose: [illegible] The following dosage chart may be used as a guide.

DOSAGE CHART

Dog Wt. lb	Dog Wt. kg	Dose Volume (mL/Dose)	Dog Wt. lb	Dog Wt. kg	Dose Volume (mL/Dose)
11	5	0.25	77	35	1.75
22	10	0.50	88	40	2.00
33	15	0.75	99	45	2.25
44	20	1.00	110	50	2.50
55	25	1.25	121	55	2.75
66	30	1.50	132	60	3.00

Injection Technique: [illegible] **CONSTITUTION PROCEDURES** [illegible]

[illegible]

CONTRAINDICATIONS

ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug.

HUMAN WARNINGS

Not for human use. Keep this and all drugs out of the reach of children.

[illegible]

WARNINGS

[illegible]

[illegible]

PRECAUTIONS

[illegible]

[illegible]

[illegible]

[illegible]

ADVERSE REACTIONS

[illegible]

[illegible]

[illegible]

[illegible]

ANIMAL SAFETY

[illegible]

[illegible]

[illegible]

Injection Site Reactions: [illegible]

[illegible]

[illegible]

CONSTITUTION PROCEDURES

The two-part ProHeart 6 product must be mixed at least 30 minutes prior to the intended time of use.

Items needed to constitute ProHeart 6:
- Microspheres (vial 1)
- Sterile 20 mL syringe for transfer
- Enclosed vent needle (25G)
- Transfer needle (18G or 20G)
- Vehicle (vial 2)

Constitution of the 20 mL vial product:

1. [illegible]
2. Using an 18G or 20G needle and sterile syringe withdraw 17.0 mL of the vehicle from the vial. [illegible] 17.0 mL removed.
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the vehicle has been added, remove the vent and transfer needles from the microsphere vial. [illegible]
6. [illegible]
7. [illegible]
8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
9. Before *every* use, gently swirl the mixture to achieve uniform suspension. [illegible]
10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. [illegible]
11. [illegible]

STORAGE INFORMATION

[illegible]

HOW SUPPLIED

ProHeart 6 is available in the following two package sizes:

1. 5-Pack
   NDC 0856-3670-2[illegible] – 20 mL vial product
   5 – 10% moxidectin sterile microspheres – 594 mg/vial
   5 – Sterile vehicle – 17 mL/vial
2. 10-Pack
   NDC 0856-3670-[illegible] – 20 mL vial product
   10 – 10% moxidectin sterile microspheres – 594 mg/vial
   10 – Sterile vehicle – 17 mL/vial

For customer service, product information or to obtain a copy of the MSDS, call (800) 533-8536

U.S. Patent No. [illegible]

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

01026 Revised April 2006 3670G

ProHeart® 6

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NADA 141-189, Approved by FDA

FORT DODGE®

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(moxidectin)

Sustained Release Injectable for Dogs

CAUTION

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

ProHeart 6 (moxidectin) Sustained Release Injectable consists of two separate vials. Vial 1 contains 10% moxidectin sterile microspheres and Vial 2 contains a specifically formulated sterile vehicle for constitution with Vial 1. No other diluent should be used. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 3.4 mg moxidectin, 3.1% glyceryl tristearate, 2.4% hydroxypropyl methylcellulose, 0.87% sodium chloride, 0.17% methylparaben, 0.02% propylparaben and 0.001% butylated hydroxytoluene. Hydrochloric acid is used to adjust pH.

PHARMACOLOGY

Moxidectin is a semi-synthetic methoxime derivative of nemadectin which is a fermentation product of *Streptomyces cyaneogriseus* subspecies *noncyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrolide.

Moxidectin has activity resulting in paralysis and death of affected parasites. The stage of the canine heartworm affected at the recommended dose rate of 0.17 mg moxidectin/kg body weight is the tissue larval stage. The larval and adult stages of the canine hookworms, *Ancylostoma caninum* and *Uncinaria stenocephala*, are susceptible.

Following injection with ProHeart 6, peak moxidectin blood levels will be observed approximately 7-14 days after treatment. At the end of the six month dosing interval, residual drug concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

INDICATIONS

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.

DOSAGE AND ADMINISTRATION

Frequency of Treatment: ProHeart 6 prevents infection by *D. immitis* for six months. It should be administered within one month of the dog's first exposure to mosquitoes. Follow-up treatments may be given every six months if the dog has continued exposure to mosquitoes and if the dog continues to be healthy without weight loss. When replacing another heartworm preventive product, ProHeart 6 should be given within one month of the last dose of the former medication.

ProHeart 6 eliminates the larval and adult stages of *A. caninum* and *U. stenocephala* present at the time of treatment. However, persistent effectiveness has not been established for this indication. Re-infection with *A. caninum* and *U. stenocephala* may occur sooner than 6 months.

Dose: The recommended subcutaneous dose is 0.05 mL of the constituted suspension/kg body weight (0.0227 mL/lb.). This amount of suspension will provide 0.17 mg moxidectin/kg bodyweight (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. The following dosage chart may be used as a guide.

DOSAGE CHART

Dog Wt.		Dose Volume	Dog Wt.		Dose Volume
lb	kg	mL/Dog	lb	kg	mL/Dog
11	5	0.25	77	35	1.75
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44	20	1.00	110	50	2.50
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66	30	1.50	132	60	3.00

Injection Technique: The two-part sustained release product must be mixed at least 30 minutes prior to the intended time of use (See **CONSTITUTION PROCEDURES** for initial mixing instructions). Once constituted, swirl the bottle gently before every use to uniformly re-suspend the microspheres. Withdraw 0.05 mL of suspension/kg body weight into an appropriately sized syringe fitted with an 18G or 20G hypodermic needle. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

Using aseptic technique, inject the product subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3 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.

CONTRAINDICATIONS

ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug.

HUMAN WARNINGS

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.

WARNINGS

Do not administer ProHeart 6 within 1 month of vaccinations. ProHeart 6 should be administered with caution in dogs with pre-existing allergic disease, including food allergy, atopy, and flea allergy dermatitis. In some cases, anaphylactic reactions have resulted in liver disease and death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products.

Owners should be given the Client Information Sheet for ProHeart® 6 to read before the drug is administered and should be advised to observe their dogs for potential drug toxicity described in the sheet. Do not administer ProHeart 6 to dogs who are sick, debilitated, underweight or who have a history of weight loss.

PRECAUTIONS

ProHeart 6 should not be used more frequently than every 6 months.

The safety and effectiveness of ProHeart 6 has not been evaluated in dogs less than 6 months of age.

Caution should be used when administering ProHeart 6 to heartworm positive dogs (See **ADVERSE REACTIONS**).

Prior to administration of ProHeart 6, dogs should be tested for existing heartworm infections. Infected dogs should be treated to remove adult heartworms. ProHeart 6 is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, ProHeart 6 is not effective for microfilariae clearance.

ADVERSE REACTIONS

In field studies, the following adverse reactions were observed in dogs treated with ProHeart 6: anaphylaxis, vomiting, diarrhea (with and without blood), listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature. Dogs with clinically significant weight loss (>10%) were more likely to experience a severe adverse reaction.

In a laboratory effectiveness study, dogs with 4- and 6-month-old heartworm infections experienced vomiting, lethargy and bloody diarrhea. These signs were more severe in the dogs with 4-month-old heartworm infections, including one dog that was recumbent and required supportive care, than in the dogs with older (6-month-old) infections.

Post-Approval Experience (March 2008): The following adverse reactions are based on voluntary post-approval drug experience reporting. The categories are listed in decreasing order of frequency by body system:

General: Anaphylaxis/toid reactions, depression/lethargy, anorexia, fever, weight loss.

Gastrointestinal: Vomiting (with and without blood), diarrhea (with and without blood), hypersalivation.

Neurological: Convulsions, ataxia, trembling, hind limb paresis

[illegible] edema, injection site pruritis/swelling, erythema multiforme.

[illegible] sized syringe fitted with an 18G or 20G hypodermic needle. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

Using aseptic technique, inject the product subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3 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.

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General: Anaphylaxis/toid reactions, depression/lethargy, anorexia, fever, weight loss.

Gastrointestinal: Vomiting (with and without blood), diarrhea (with and without blood), hypersalivation.

Neurological: Convulsions, ataxia, trembling, hind limb paresis

Dermatological: Urticaria, head/facial edema, injection site pruritis/swelling, erythema multiforme.

Hematological: Immune-mediated hemolytic anemia, leukocytosis, immune-mediated thrombocytopenia

Hepatic: Elevated liver enzymes, hepatopathy, hypoproteinemia, hyperbilirubinemia.

Respiratory: Dyspnea, polypnea, coughing.

Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

In rare situations, death has been reported as an outcome of the adverse events listed above.

To report suspected adverse reactions or to obtain technical assistance, call (800) 533-8536.

ANIMAL SAFETY

General Safety: ProHeart 6 has been administered to a wide variety of healthy dogs six months of age and older, including a wide variety of breeds, pregnant and lactating females, breeding males, and ivermectin-sensitive collies. In clinical studies, 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 (see **WARNINGS**).

ProHeart 6 administered at 3 times the recommended dose in dogs with patent heartworm infections and up to 5 times the recommended dose in ivermectin-sensitive collies did not cause any adverse reactions. ProHeart 6 administered at 3 times the recommended dose did not adversely affect the reproductive performance of male or female dogs. ProHeart 6 administered up to 5 times the recommended dose in 7-8 month old puppies did not cause any systemic adverse effects.

In well controlled clinical field studies, ProHeart 6 was used in conjunction with a variety of veterinary products including anthelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics and flea control products.

Injection Site Reactions: Injection site observations were recorded during effectiveness and safety studies. In clinical studies, ProHeart 6 was administered at six-month intervals to client-owned dogs under field conditions. There were no reports of injection site reactions in these field studies and evaluations of the injection sites revealed no abnormalities.

In a laboratory safety study, ProHeart 6 was administered at 1, 3 and 5 times the recommended dose to 7-8 month old puppies. Injection sites were clipped to facilitate observation. Slight swelling/edema at the injection site was observed in some dogs from all treated groups. These injection site reactions appeared as quickly as 8 hours post injection and lasted up to 3 weeks. A three-year repeated injection study was conducted to evaluate the safety of up to 6 injections of ProHeart 6 administered at the recommended dose (0.17 mg/kg) every 6 months. Mild erythema and localized deep subcuticular thickening were seen in dogs that received four injections in the same area on the neck and in one dog that received two injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous panniculitis with microvacuolation. The only adverse reaction seen that was not related to the injection site was weight loss in one dog.

Some dogs treated with ProHeart 6 in laboratory effectiveness studies developed transient, localized inflammatory injection site reactions. These injection site reactions were visible grossly for up to 3 weeks after injection. Histologically, well-defined granulomas were observed in some dogs at approximately 5 months after injection.

CONSTITUTION PROCEDURES

The two-part ProHeart 6 product must be mixed at least 30 minutes prior to the intended time of use.

Items needed to constitute ProHeart 6:

- Microspheres (vial 1)
- Sterile 20 mL syringe for transfer
- Enclosed vent needle (25G)
- Transfer needle (18G or 20G)
- Vehicle (vial 2)

Constitution of the 20 mL vial product.

1. Shake the microsphere vial to break up any aggregates prior to constitution.
2. Using an 18G or 20G needle and sterile syringe withdraw 17.0 mL of the unique vehicle from the vial. **There is more vehicle supplied than the 17.0 mL required.**
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the vehicle has been added, remove the vent and transfer needles from the microsphere vial. Discard unused vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.
7. Record the time and date of mixing on the microsphere vial.
8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
9. Before <u>every</u> use, gently swirl the mixture to achieve uniform suspension. The microspheres and vehicle will gradually separate on standing.
10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.
11. Refrigerate the unused product. The constituted product remains stable for 4 weeks in a refrigerator. Avoid direct sunlight.

STORAGE INFORMATION

Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After constitution, the product is stable for 4 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

ProHeart 6 is available in the following two package sizes.

1. 5-Pack
   NDC 0856-3670-25 – 20 mL vial product:
   5 - 10% moxidectin sterile microspheres - 598 mg/vial
   5 - Sterile vehicle - 17 mL/vial
2. 10-Pack
   NDC 0856-3670-29 – 20 mL vial product:
   10 - 10% moxidectin sterile microspheres - 598 mg/vial
   10 - Sterile vehicle - 17 mL/vial

For customer service, product information or to obtain a copy of the MSDS, call (800) 533-8536.

U.S. Patent No. 4,916,154 and 6,340,671

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA