



Fort Dodge Animal Health
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Dear Doctor:

This letter is to provide another update of our field experiences with ProHeart® 6 (moxidectin) as we pass the two year anniversary of its launch, and some label additions being made to reflect some of these experiences, as noted below. We trust that this information will be useful and encourage you to call our Professional Services department if you have any additional questions after reviewing this material.

There are two additions to the ProHeart 6 label that have either been made, or are in the process of being made. The first was the label change regarding use of ProHeart 6 in heartworm-positive dogs. Briefly, the changes were made in response to a low number of heartworm-positive dogs that experienced coughing or cardiopulmonary signs after receiving ProHeart 6. The pre-approval clinical studies did not identify any such reactions prior to release, and many heartworm-positive dogs have received ProHeart 6 without side effects. However, based on reports received on a low number of heartworm-positive dogs, Fort Dodge, in conjunction with the Center for Veterinary Medicine, made the following changes:

Under the heading "Post Approval Experience," the following statement was added:

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

Additional labeling changes made under the "Precautions" section of the package insert and printed cartons in conjunction with this statement included:

1. Removal of the statement "At the discretion of the veterinarian" before the sentence "Infected dogs should be treated to remove adult heartworms."
2. The following statement was deleted "No adverse reactions were observed in dogs with patent heartworm infections when ProHeart 6 was administered at three times the labeled dose. Higher doses were not tested." (A similar statement was already present in the Animal Safety section, and this statement was left unchanged.)

The second label change is the recent decision to add a statement regarding the rare occurrence of death in a low number of dogs treated with ProHeart 6. Death has been reported in approximately 0.0025 percent of the doses sold into veterinary clinics. Some of the reports are associated with severe allergic events, while others appear to be multifactorial in nature. Some are linked to factors not associated with product use.

We continue to investigate all reports as fully as possible. If and when further information becomes available that has clinical implications on product use, we will advise the veterinary community accordingly.

With regard to the label change, the following new statement, "and rare reports of death" has been added to the "Post-Approval Experience" section under the heading "ADVERSE REACTIONS." The full "Post-Approval Experience" section now reads:

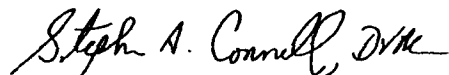
Post-Approval Experience: Although not all adverse events are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toid reactions, depression/lethargy, urticaria, head/facial edema, and rare reports of death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

This revised "Post-Approval Experience" statement will replace the current wording, which appears in the ProHeart 6 package insert and on all approved ProHeart 6 printed outer boxes.

In order to help educate your clients on both the benefits and potential side effects associated with ProHeart[®] 6 (moxidectin), Fort Dodge Animal Health has prepared a client information sheet which contains questions and answers about use of the product, and includes the product insert on the reverse side. An example copy is attached for your reference. Additional quantities will be available to you through your Fort Dodge representative and the sheet will soon be posted on our websites for both veterinarians and clients to download and print.

Thank you for your attention to this important information. We feel it is essential to provide you with timely updates on the use of this product. Millions of doses of ProHeart 6 continue to be used safely, and we trust that this reflects your on-going experience, as well. We continue our monitoring activities and will provide any pertinent updates on ProHeart 6 as they become available. Please feel free to contact one of our Professional Services veterinarians at the number listed above if you have additional questions or concerns regarding any of this information.

Sincerely,



Stephen A. Connell, DVM

Vice President,

Professional and Technical Services

Client Information about ProHeart® 6 (moxidectin)

ProHeart 6 (pronounced "Pro-hart" "six")

Generic name: moxidectin ("mox-ee-deck-tin")

This summary contains important information about ProHeart 6. You should read this information before your veterinarian administers ProHeart 6 to your dog and review it each time your dog is retreated. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about ProHeart 6.

What is ProHeart 6?

ProHeart 6 is an injectable parasiticide that is used in dogs six months of age and older to prevent heartworm disease and treat common hookworm infections.

Why has my veterinarian prescribed ProHeart 6?

ProHeart 6 has been prescribed by your veterinarian to treat or prevent the following parasites in your dog:

- Continuous prevention of heartworm disease for six months (*Dirofilaria immitis*)
- Treatment of common hookworm infections (*Ancylostoma caninum* and *Uncinaria stenocephala*)

What should I discuss with my veterinarian before ProHeart 6 is prescribed?

Your veterinarian is your best resource for recommending appropriate medications for your pet. It is important to discuss your dog's health history with your veterinarian so he/she can decide if ProHeart 6 is right for your pet.

Which dogs should not be treated with ProHeart 6?

ProHeart 6 should be used with caution in sick, debilitated and underweight animals. Dogs should be tested for heartworm disease prior to being treated with ProHeart 6. If your dog tests positive for adult heartworms your veterinarian should treat the infection with an appropriate medication before administering ProHeart 6.

What are the possible side effects of ProHeart 6?

Like most medicines, side effects following ProHeart 6 administration have occasionally been reported. These can include (but are not limited to) allergic responses, lethargy (sluggishness), seizures, vomiting and diarrhea, itching at the injection site, fever and, in rare instances, death. If you have additional questions about potential side effects, talk to your veterinarian.

Can ProHeart 6 be given with other medicines?

In well-controlled clinical studies, ProHeart 6 was used safely in dogs receiving other veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics, and flea control products. Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to use with ProHeart 6.

How long will ProHeart 6 remain in the body?

Several studies have shown that by the end of the six-month treatment period, the amount of ProHeart 6 remaining in the body is too small to measure. An additional study demonstrated that after four consecutive treatments there was no accumulation of ProHeart 6 over time.

What else should I know about ProHeart 6?

This sheet provides a summary of information about ProHeart 6. If you have any questions or concerns about ProHeart 6, talk to your veterinarian. Read the package insert for more information. To obtain additional information visit the website at www.proheart6.com, or call 1-800-685-5656.

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

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 3.1 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 cyanogriseus* subsp. *non-cyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrocyclic.

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. 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	mL/Dog	kg	mL/Dog
11	0.25	77	3.5
22	0.50	88	4.0
33	0.75	99	4.5
44	1.00	110	5.0
55	1.25	121	5.5
66	1.50	132	6.0

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.

PRECAUTIONS

Use with caution in sick, debilitated or underweight animals (see SAFETY).

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.

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 approximately 1% of 280 dogs treated with ProHeart 6: vomiting, diarrhea, listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature.

Post-Approval Experience: Although not all adverse reactions are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toid reactions, depression/lethargy, urticaria, head/face edema, and rare reports of death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

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

ANIMAL SAFETY

General Safety: ProHeart 6 has been safely 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. However, 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 PRECAUTIONS).

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 safely used in conjunction with a variety of veterinary products including vaccines, 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.

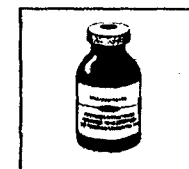
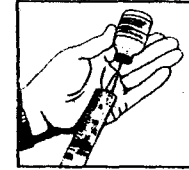
CONSTITUTION PROCEDURES

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
- Vehicle (vial 2)
- Enclosed vent needle (25G)
- Transfer needle (18G or 20G)

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 every 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) 685-5856.

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

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