SATISFACTION GUARANTEE

ProHeart® 12 (moxidectin) | ProHeart® 6 (moxidectin)

If you feel that ProHeart® 12 (moxidectin) or ProHeart® 6 (moxidectin) is not providing sufficient protection for the indications for which it is labeled, please call our medical support team to discuss our ProHeart Satisfaction Guarantee. Zoetis will work with you to ensure that you are satisfied with the performance of ProHeart or we will refund you the purchase price.*

The ProHeart Satisfaction Guarantee is available to individuals who have purchased ProHeart from, and have had ProHeart administered by, a ProHeart-certified licensed veterinarian, technician, or staff member. All claims are evaluated on a case-by-case basis based on the program guidelines and requirements outlined below.

1. Heartworm Disease Guidelines: If any dog determined by a licensed veterinarian to be free of heartworm infection at the onset of treatment with ProHeart develops heartworm disease, we will provide reimbursement (up to $1000 and the acquisition cost of melarsomine dihydrochloride) associated with the diagnosis and treatment of heartworm disease and provide a year's supply of ProHeart.

2. Hookworms, roundworms, tapeworms and whipworms: ProHeart treats adult and larval hookworm infections existing at the time of administration. ProHeart is not effective against and does not have label indications to treat roundworm, tapeworm, or whipworm infections. However, if you are administering ProHeart and a dog tests positive for any of these parasites, Zoetis will pay the reasonable and customary costs up to $100 for an approved treatment. The veterinarian may determine the appropriate treatment.

Program requirements:

- ProHeart was administered according to the label directions by a ProHeart-certified veterinary heath professional.
- The use of a *Dirofilaria immitis* antigen test will be the standard for determining heartworm status. Knott's or any filter test for the detection of microfilaria will not provide sufficient evidence for pretreatment heartworm negative status.
- Two separate blood samples using at least two different brands of antigen tests are required to document heartworm positive status.
- Dogs previously treated for heartworm disease must have a negative antigen test prior to starting ProHeart 12 or ProHeart 6.
- Dogs starting or changing heartworm preventatives are required to have two negative antigen tests at least six months apart after initiation of ProHeart 12 or ProHeart 6 administration.‡

IMPORTANT SAFETY INFORMATION: Use ProHeart 6 in dogs 6 months of age or older and ProHeart 12 in dogs 12 months of age or older. Do not administer to dogs that are sick, debilitated, underweight, have a history of weight loss, or to those previously found to be hypersensitive to the drug. Hypersensitivity reactions may occur in some dogs when ProHeart is administered alone or with vaccines. Anaphylactic and anaphylactoid reactions can result in death and should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. Reported side effects in clinical trials included vomiting, lethargy, diarrhea, anorexia, and hypersensitivity reactions. People should avoid inhalation, contact with eyes, or accidental self-injection. See full Prescribing Information for ProHeart 6 and ProHeart 12, attached.

ProHeart is available only to veterinarians through a restricted distribution program. Only ProHeart-certified veterinarians, technicians and staff can administer it. To obtain additional information including a copy of the product labeling, visit proheartdvm. com or call 1-888-ZOETIS1 (963-8471).

Zoetis reserves the right to modify or discontinue this program at any time for any reason. Call the Zoetis Veterinary Medical Information & Product Support team with Satisfaction Guarantee questions at 1-888-963-8471.

* Subject to program requirements as outlined in this document.
**Guarantee applies to current product purchased from a veterinary hospital and administered by a licensed ProHeart-certified veterinarian, technician or staff member only.
‡ Dogs that have not previously received heartworm prevention, or those that have received inconsistent heartworm prevention, prior to starting ProHeart may test negative when therapy is initiated despite being infected. This may occur due to very low worm burdens, the inability of antigen heartworm tests to reliably detect infections less than five months post-infection, as well as the potential of macrocyclic lactones to delay the development of heartworms. As such, a single test—or two tests separated by six months after the initiation of a preventative regimen—will miss some infections. At this time, the American Heartworm Society recommends three consecutive "negative" antigen tests six months apart to potentially classify dogs as heartworm disease "negative."[1,2]

References: 1. Heartworm preventive resistance: Is it possible? American Heartworm Society. https://www.heartwormsociety.org/in-the-news/81-heartworm-preventive-resistance-is-it-possible. Updated December 5, 2013. Accessed January 7, 2025. **2.** Prevention, Diagnosis, and Management of Heartworm Infection (*Dirofilaria immitis*) in Dogs, Revised 2024. Accessed January 7, 2025. https://d3ft8sckhnqim2.cloudfront.net/images/AHS_Canine_Guidelinesweb22NOV2024.pdf.

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ProHeart® 12 (moxidectin)

For Extended-Release Injectable Suspension for Dogs

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

DESCRIPTION
ProHeart 12 (moxidectin) for extended-release injectable suspension consists of two separate vials: one vial contains 10% moxidectin sterile microspheres; and the second vial contains a specifically formulated sterile vehicle for constitution with the microspheres. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 10 mg moxidectin, 9% glyceryl tristearate, 2.25% hydroxypropyl methylcellulose, 0.81% sodium chloride, 0.16% methylparaben, 0.02% propylparaben and 0.004% butylated hydroxytoluene. Hydrochloric acid is used to adjust pH. The constituted product may appear as a hazy to milky suspension.

INDICATIONS
ProHeart 12 is indicated for use in dogs 12 months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis* for 12 months.
ProHeart 12 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

DOSAGE AND ADMINISTRATION
Always provide Client Information Sheet and review with owners before administering ProHeart 12. The owner should be advised to observe their dog for adverse drug events including those described on the sheet. The Client Information Sheet is attached to this package insert and available online at http://www.proheart12.com for reprinting to provide to the owner.

Frequency of Treatment:
ProHeart 12 prevents the development of heartworm disease caused by *D. immitis* for 12 months. For dogs not previously on heartworm preventive or having lapsed beyond 12 months of a prior ProHeart 12 dose, the product should be given within 1 month of exposure to mosquitoes. Follow-up treatments may be given every 12 months, if the dog continues to be healthy and without weight loss, to provide continuous year-round protection. When replacing a monthly heartworm preventive product, ProHeart 12 should be given within one month of the last dose of the former medication to avoid a gap in protection.

ProHeart 12 eliminates the larval and adult stages of *A. caninum* and *U. stenocephala* present at the time of treatment. Re-infection with *A. caninum* and *U. stenocephala* may occur sooner than 12 months.

Dose: The recommended subcutaneous dose is 0.05 mL of the constituted suspension/kg body weight (0.023 mL/lb). This amount of suspension will provide 0.5 mg moxidectin/kg body weight (0.23 mg/lb). To ensure accurate dosing, calculate each dose based on the dog's weight at the time of treatment. The following table provides a guide for weight specific dose volumes.

Table 1: Dosage Guide

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

*All dogs should be dosed at 0.05 mL suspension/kg body weight (0.023 mL /lb).

Injection Technique:
ProHeart 12 must be prepared at least 30 minutes prior to the first use by adding the sterile vehicle to the microspheres. (See **CONSTITUTION PROCEDURES** for initial mixing instructions.)

Swirl the constituted product vial gently before every use to uniformly re-suspend the microspheres.

Withdraw 0.05 mL of suspension/kg body weight (0.023 mL/lb) 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.

RISK MINIMIZATION ACTION PLAN
The ProHeart 12 and ProHeart 6 Risk Minimization Action Plan (RiskMAP) provides educational materials to the veterinarian, veterinary staff, and the dog owner explaining the risks and proper use of ProHeart 12 and ProHeart 6. ProHeart 12 and ProHeart 6 are the same formulation, but ProHeart 12 is three times the concentration of ProHeart 6. ProHeart 12 and ProHeart 6 are for use in dogs only and are available through a restricted distribution program to veterinarians that have completed the RiskMAP training and certification module.

The ProHeart 12 and ProHeart 6 web-based training and certification module is available at http://www.proheart12.com. This website has important information on the safe and effective use of ProHeart 12 and ProHeart 6 for veterinarians.

Only veterinarians and veterinary technicians/assistants that have completed the training and are certified can administer ProHeart 12 and ProHeart 6. Veterinarians are expected to report all adverse events that occur in animals or humans to the manufacturer. Important safety information is included below:

CONTRAINDICATIONS
ProHeart 12 is contraindicated in animals previously found to be hypersensitive to this drug or ProHeart 6.

HUMAN WARNINGS
Not for human use. Keep this and all drugs out of the reach of children.
If contact with your skin occurs, wash thoroughly with water. May be irritating to the eyes. If product accidentally gets into your eyes, flush eyes thoroughly with water. In case of accidental ingestion, or if skin or eye irritation occurs, contact a Poison Control Center or physician for treatment advice and show the package insert to the physician.

Take care to avoid accidental self-injection. In case of accidental self-injection, seek medical advice and show the package insert or the label to the physician. The Safety Data Sheet (SDS) contains more detailed occupational safety information.

WARNINGS
Anaphylactic and anaphylactoid reactions may occur in some dogs following administration of ProHeart 12 alone or with vaccines. In some cases, these reactions have resulted in death following administration of moxidectin microspheres (see **POST-APPROVAL EXPERIENCE**). Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products.

Always provide Client Information Sheet and review with owners before administering ProHeart 12. The owner should be advised to observe their dog for adverse drug events including those described on the sheet.

Do not administer ProHeart 12 to dogs who are sick, debilitated, underweight or who have a history of weight loss.

PRECAUTIONS
Prior to administration of ProHeart 12, the health of the patient should be assessed by a thorough medical history, physical examination and diagnostic testing as indicated (see **WARNINGS**).

Caution should be used when administering ProHeart 12 in dogs with pre-existing allergic disease, including food allergy, atopy, and flea allergy dermatitis. (see **WARNINGS**).

Caution should be used when administering ProHeart 12 concurrently with vaccinations. Adverse reactions, including anaphylaxis, have been reported following the concomitant use of moxidectin microspheres and vaccinations (see **WARNINGS** and **POST-APPROVAL EXPERIENCE**).

ProHeart 12 should not be used more frequently than every 12 months.

The effectiveness of ProHeart 12 has not been evaluated in dogs less than 12 months of age.

Prior to administration of ProHeart 12, dogs should be tested for existing heartworm infections. Infected dogs should be treated with an adulticide to remove adult heartworms. ProHeart 12 is not effective against adult *D. immitis*.

Caution should be used when administering ProHeart 12 to heartworm positive dogs (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS
A well-controlled field study was conducted, including a total of 593 dogs (297 received two doses of ProHeart 12, 12 months apart and 296 received a monthly oral heartworm preventive as active control) ranging in age from 1 to 14 years. Over the 605-day study period, all observations of potential adverse reactions were recorded.

Table 2: Number of Dogs* with Adverse Reactions Reported During the ProHeart 12 Field Study

Adverse Reaction	ProHeart® 12 n=297 (%)	Active Control n=296 (%)
Vomiting	75 (25.3)	78 (26.4)
Lethargy	46 (15.5)	34 (11.5)
Diarrhea (with and without blood)	43 (14.5)	46 (15.5)
Anorexia	41 (13.8)	31 (10.5)
Seizures	10 (3.4)	7 (2.4)
Hepatopathy	8 (2.7)	3 (1.0)
Hypersalivation	7 (2.4)	3 (1.0)
Anaphylactoid/Hypersensitivity Reactions	6 (2.0)	4 (1.4)

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Two ProHeart 12 (moxidectin) - treated dogs experienced anaphylactoid/hypersensitivity-related clinical signs within the first 24 hours following the initial treatment. Both dogs responded to symptomatic treatment. One dog experienced hives and facial swelling that resolved in 24 hours. The second dog experienced redness and swelling of the face and paws, followed by vomiting, polydipsia, and elevated heart rate and was treated symptomatically. Signs resolved within 4 days. One dog was pre-treated before the second injection of ProHeart 12, and neither dog had a reaction to the second dose 12 months later. One active control-treated dog experienced anaphylactoid/hypersensitivity-related clinical signs within the first 24 hours. The dog was withdrawn from the study prior to the second monthly dose.

Mild injection site reactions occurred in six ProHeart 12-treated dogs and were observed from one to seven days post dosing and included warmth, swelling and pruritus. One of these cases included mild pruritus at the injection site that resolved spontaneously within 24 hours of administration.

In a laboratory effectiveness study, dogs with 4- and 6-month-old heartworm infections administered moxidectin microspheres at a dose of 0.17 mg/kg 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 (2018): The following adverse events are based on post-approval adverse drug experience reporting for ProHeart 6. ProHeart 12 and ProHeart 6 are the same formulation, but ProHeart 12 is three times the concentration of ProHeart 6. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Immune: anaphylaxis and/or anaphylactoid reactions, urticaria, head/facial edema, pruritus, pale mucous membranes, collapse, cardiovascular shock, erythema, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia (signs reflected in other system categories could be related to allergic reactions, i.e. gastrointestinal, dermatologic, and hematologic)
Gastrointestinal: vomiting (with or without blood), diarrhea with or without blood, hypersalivation
General: depression, lethargy, anorexia, fever, weight loss, weakness
Dermatological: injection site pruritus/swelling, erythema multiforme
Neurological: seizures, ataxia, trembling, hind limb paresis
Hematological: leukocytosis, anemia, thrombocytopenia
Respiratory: dyspnea, tachypnea, coughing
Hepatic: elevated liver enzymes, hypoproteinemia, hyperbilirubinemia, hepatopathy
Urinary: elevated BUN, elevated creatinine, hematuria, polydipsia, polyuria
Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm positive dogs.

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

Foreign market experience with ProHeart 12 includes similar voluntarily reported adverse events, including death, following administration of ProHeart 12.

For a copy of the Safety Data Sheet (SDS) or to report suspected adverse reactions, contact Zoetis at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

INFORMATION FOR DOG OWNERS

Always provide Client Information Sheet and review with owners before administering ProHeart 12. Owners should be advised of the potential for adverse reactions, including anaphylaxis, and be informed of the clinical signs associated with drug toxicity (see **WARNINGS, ADVERSE REACTIONS** and **POST-APPROVAL EXPERIENCE** sections.)

Owners should be advised to contact their veterinarian immediately if signs of toxicity are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized and veterinary care, if appropriate, is initiated.

CLINICAL 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 0.5 mg/kg (0.23 mg/lb) is the tissue larval stage. The larval and adult stages of the canine hookworms, *A. caninum* and *U. stenocephala*, are susceptible.

Following injection with ProHeart 12, peak moxidectin blood levels will be observed approximately 7-14 days after treatment. At the end of the 12-month dosing interval, residual drug plasma concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

EFFECTIVENESS

Prevention of Heartworm:
In two separate well-controlled laboratory studies, ProHeart 12 administered at a dose of 0.5 mg/kg (0.23 mg/lb), demonstrated 100% effectiveness in preventing the development of *D. immitis* in dogs inoculated with infective larvae 365 days after treatment.

In a well-controlled 605-day US field study, two doses of ProHeart 12 were administered subcutaneously at a dosage of 0.5 mg/kg (0.23 mg/lb), 12 months apart. A total of 235, 226 and 222 ProHeart 12-treated dogs completed the heartworm testing (adult heartworm antigen and microfilariae) on Days 365, 480 and 605, respectively. None of these dogs tested positive for heartworm on any of the test days.

Treatment of Existing Larval and Adult Hookworms:
Seven well-controlled laboratory studies conducted with moxidectin microspheres at a dose of 0.17 mg/kg confirm the effectiveness against natural infections and induced infections of larval and adult *A. caninum* and *U. stenocephala*. All studies demonstrated ≥ 90% effectiveness against the respective hookworm species.

ANIMAL SAFETY

Margin of Safety: ProHeart 12 was subcutaneously administered to Beagle dogs (8 dogs per group) at 1X, 3X, and 5X the recommended dose of 0.5 mg/kg body weight on Days 1, 183, and 365. The control group (8 dogs) received saline injections. ProHeart 12 was well tolerated and did not result in any adverse systemic effects. ProHeart 12-related findings included edema and thickening of the injection site.

Ivermectin-Sensitive Collie Safety: In a laboratory study, 15 ivermectin-sensitive Collie dogs in three treatment groups were administered one dose of saline and one dose of ProHeart 12, 21 days apart. Each dog served as its own control and the order of administration of the saline and ProHeart 12 varied by treatment group. ProHeart 12 was dosed at 0.5 mg/kg body weight (1X, five dogs), 1.5 mg/kg body weight (3X, five dogs), or 2.5 mg/kg body weight (5X, five dogs). No clinical signs of moxidectin toxicity were observed during the 42-day study.

Heartworm-Positive Safety: In a laboratory study, 16 Beagle dogs implanted with adult heartworms (*D. immitis*) received either ProHeart 12 at 1.5 mg/kg body weight (3X, 8 dogs) or a saline injection (control, 8 dogs). At 119 days post-infection (56 days post-moxidectin treatment), no adverse clinical signs and no gross pathological effects were noted in dogs with induced adult heartworm infections.

Reproductive Safety:

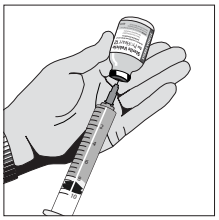
Females: A reproductive laboratory study in 40 female Beagle dogs assessed the safety of ProHeart 12 at a single 1.5 mg/kg body weight (3X) dose. The dogs were divided into four treatment groups of 8 dogs per group to cover the critical periods of the reproductive cycle (pre-mating, mating, mid-gestation, and lactation). The control group (8 dogs) were untreated. No adverse effects in terms of conception, pregnancy maintenance, and the development, growth, and health of the puppies were observed through puppy weaning at 6 weeks of age.

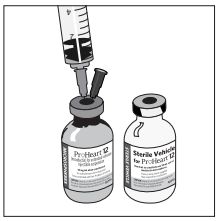
Males: A reproductive laboratory study assessed the safety of ProHeart 12 in eight male Beagle dogs at a single 1.5 mg/kg body weight (3X) dose. The control group (8 dogs) received a saline injection. No adverse reactions were noted in any of the dogs during the 91-day study. No clinically significant changes or abnormalities were noted in semen quality. Minor injection site thickening was noted by palpation in four dogs; all resolved within 13 weeks.

CONSTITUTION PROCEDURES

ProHeart 12 must be prepared at least 30 minutes prior to the first use.
Items needed to constitute ProHeart 12 10 mL (889 mg) product (9 mL when constituted):

- Sterile vehicle vial- included
- Microspheres vial- included
- Vent needle (25G)- included
- Sterile 10 mL syringe for transfer- not included
- Transfer needle (18G or 20G) - not included





Constitution of the 10 mL vial product (9 mL when constituted).

1. Shake the microsphere vial to break up any aggregates prior to constitution.
2. Using an 18G or 20G needle and sterile syringe withdraw 8 mL of the unique sterile vehicle from the vial.
   There is more sterile vehicle supplied than the 8 mL required.
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the 8 mL of sterile vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the sterile vehicle has been added, remove the vent and transfer needles from the microsphere vial.
   Discard unused sterile vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.
   The product may appear as a hazy to milky suspension.
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 product may appear as a hazy to milky 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 8 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 8 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

ProHeart 12 10 mL vial product is available in the following package sizes.

1-Pack	5-Pack	10-Pack
1 - 10% moxidectin sterile microspheres- 889 mg/vial 1 - Sterile vehicle - 8 mL/vial	5 - 10% moxidectin sterile microspheres- 889 mg/vial 5 - Sterile vehicle - 8 mL/vial	10 - 10% moxidectin sterile microspheres- 889 mg/vial 10 - Sterile vehicle - 8 mL/vial

Approved by FDA under NADA # 141-519
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Distributed by: Zoetis Inc., Kalamazoo, MI 49007 40031204A&P

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ProHeart® 6 (moxidectin)

For Extended-Release Injectable Suspension 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) for extended-release injectable suspension consists of two separate vials: One vial contains 10% moxidectin sterile microspheres and the second vial contains a specifically formulated sterile vehicle for constitution with the microspheres. 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. The constituted product may appear as a hazy to milky suspension.

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* for 6 months.

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

DOSAGE AND ADMINISTRATION

Always provide Client Information Sheet and review with owners before administering ProHeart 6. The owner should be advised to observe their dog for adverse drug events including those described on the sheet.

Frequency of Treatment: ProHeart 6 prevents the development of heartworm disease caused 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
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: 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.

RISK MINIMIZATION ACTION PLAN

The ProHeart 6 and ProHeart 12 Risk Minimization Action Plan (RiskMAP) provides educational materials to the veterinarian, veterinary staff, and the dog owner explaining the risks and proper use of ProHeart 6 and ProHeart 12. ProHeart 6 and ProHeart 12 are the same formulation, but ProHeart 6 is three times less concentrated than ProHeart 12. ProHeart 6 and ProHeart 12 are for use in dogs only and are available through a restricted distribution program to veterinarians that have completed the RiskMAP training and certification module.

The ProHeart 6 and ProHeart 12 web-based training and certification module is available at http://www.proheart6.com. This website has important information on the safe and effective use of ProHeart 6 and ProHeart 12 for veterinarians.

Only veterinarians and veterinary technicians/assistants that have completed the training and are certified can administer ProHeart 6 and ProHeart 12. Veterinarians are expected to report all adverse events that occur in animals or humans to the manufacturer. Important safety information is included below:

CONTRAINDICATIONS

ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug or ProHeart 12.

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 Safety Data Sheet (SDS) contains more detailed occupational safety information.

WARNINGS

Anaphylactic and anaphylactoid reactions may occur in some dogs following administration of ProHeart 6 alone or with vaccines. In some cases, these reactions have resulted in death following administration of moxidectin microspheres (see **POST-APPROVAL EXPERIENCE**). Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products.

Always provide Client Information Sheet and review with owners before administering ProHeart 6. The owner should be advised to observe their dog for adverse drug events including those described on the sheet.

Do not administer ProHeart 6 to dogs who are sick, debilitated, underweight or who have a history of weight loss.

PRECAUTIONS

Prior to administration of ProHeart 6, the health of the patient should be assessed by a thorough medical history, physical examination and diagnostic testing as indicated (see **WARNINGS**).

Caution should be used when administering ProHeart 6 in dogs with pre-existing allergic disease, including food allergy, atopy, and flea allergy dermatitis. (see **WARNINGS**).

Caution should be used when administering ProHeart 6 concurrently with vaccinations. Adverse reactions, including anaphylaxis, have been reported following the concomitant use of moxidectin microspheres and vaccinations (see **WARNINGS** and **POST-APPROVAL EXPERIENCE**).

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

The 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 with an adulticide to remove adult heartworms. ProHeart 6 is not effective against adult *D. immitis.*

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

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 (Rev. 2018) The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Immune: anaphylaxis and/or anaphylactoid reactions, urticaria, head/facial edema, pruritus, pale mucous membranes, collapse, cardiovascular shock, erythema, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia (signs reflected in other system categories could be related to allergic reactions, i.e. gastrointestinal, dermatologic, and hematologic)

Gastrointestinal: vomiting (with or without blood), diarrhea with or without blood, hypersalivation

General: depression, lethargy, anorexia, fever, weight loss, weakness

Dermatological: injection site pruritus/swelling, erythema multiforme

Neurological: seizures, ataxia, trembling, hind limb paresis

Hematological: leukocytosis, anemia, thrombocytopenia

Respiratory: dyspnea, tachypnea, coughing

Hepatic: elevated liver enzymes, hypoproteinemia, hyperbilirubinemia, hepatopathy

Urinary: elevated BUN, elevated creatinine, hematuria, polydipsia, polyuria

Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm positive dogs.

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

For a copy of the Safety Data Sheet (SDS) or to report suspected adverse reactions, contact Zoetis at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

INFORMATION FOR DOG OWNERS

Always provide Client Information Sheet and review with owners before administering ProHeart 6. Owners should be advised of the potential for adverse reactions, including anaphylaxis, and be informed of the clinical signs associated with drug toxicity (see **WARNINGS, ADVERSE REACTIONS** and **POST-APPROVAL EXPERIENCE** sections.)

Owners should be advised to contact their veterinarian immediately if signs of toxicity are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized and veterinary care, if appropriate, is initiated.

CLINICAL 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 0.5 mg/kg (0.227 mg/lb) is the tissue larval stage.

The larval and adult stages of the canine hookworms, *A. caninum* and *U. 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 6-month dosing interval, residual drug plasma concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

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.

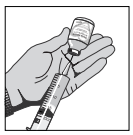
Some dogs treated with ProHeart 6 in laboratory effectiveness studies developed transient, localized inflammatory injection site reactions. These injection site reactions were visible grossly for up to 3 weeks after injection. Histologically, well-defined granulomas were observed in some dogs at approximately 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 (17.7 mL when constituted):

- Microspheres
- Sterile 20 mL syringe for transfer
- Enclosed vent needle (25G)
- Transfer needle (18G or 20G)
- Sterile vehicle



Constitution of the 20 mL vial product (17.7 mL when constituted).

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 sterile vehicle from the vial. **There is more sterile vehicle supplied than the 17.0 mL required.**
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the sterile vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the sterile vehicle has been added, remove the vent and transfer needles from the microsphere vial. Discard unused sterile vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced. The constituted product may appear as a hazy to milky suspension.
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 constituted product may appear as a hazy to milky 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 8 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 8 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

ProHeart 6 is available in the following three package sizes.

1. 1-Pack
20 mL vial product:
1 - 10% moxidectin sterile microspheres - 598 mg/vial
1 - Sterile vehicle - 17 mL/vial

2. 5-Pack
20 mL vial product:
5 - 10% moxidectin sterile microspheres - 598 mg/vial
5 - Sterile vehicle - 17 mL/vial

3. 10-Pack
20 mL vial product:
10 - 10% moxidectin sterile microspheres - 598 mg/vial
10 - Sterile vehicle - 17 mL/vial

zoetis

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