IT ONLY TAKES ONE

ONE BITE* can give a dog heartworm disease.† ONE ProHeart® 12 injection ensures ONE FULL YEAR of constant protection.

ProHeart 12 is the only once-yearly injection to prevent heartworm disease* in dogs.

*From an infected mosquito.
†Caused by Dirofilaria immitis.

Learn more at ProHeart.com
Why ProHeart 12?

Heartworm disease is serious and can be fatal.
ProHeart 12 is a simple way to give your dog a full year of protection

ProHeart 12 works by releasing protective medicine against heartworm disease for 12 months at a time for assured protection and also offers:

- Timely prevention that you can easily fit in with your dog’s yearly wellness visit
- The convenience of a once-a-year injection—so you don’t have to worry about forgetting a monthly dose and leaving your dog exposed to heartworm disease

Heartworm disease is a threat to every dog—including yours

How does heartworm disease happen?

Just a single bite from an infected mosquito is all it takes. Through that bite, your dog can get infected with young heartworms that can develop and eventually grow up to a foot long in the heart and lungs.

Heartworm disease is on the rise—here’s why

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<table>
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<tbody>
<tr>
<td>1/3</td>
<td>In the USA, only 1/3 of dogs are given heartworm disease prevention¹</td>
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<tr>
<td>📅</td>
<td>It’s easy for owners to miss doses with monthly chewables²</td>
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<tr>
<td>☀️</td>
<td>Changes in climate conditions—heartworms thrive in humid, warm environments³</td>
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<tr>
<td>🔻</td>
<td>Increased pet owner travel with dogs means increased chance for spreading heartworms abroad⁴,⁵</td>
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</tbody>
</table>

Heartworm disease has been diagnosed in dogs in every state.³

ProHeart 12—Continuous protection for your dog means continuous peace of mind for you.

With heartworm disease on the rise, prevention is a must for your dog.
Heartworm disease is preventable—but which type of prevention to choose?

There are other options to prevent heartworm disease. Monthly chewables are one choice—but are they really right for you or your dog? Consider this:

1. When life gets busy, it can be tough to stay on top of monthly dosing—and many pet owners do forget.²

2. Dogs may vomit or spit out the chews, which means you may have to redose.

3. Some dogs refuse to eat "treat-like" preventatives.

Monthly chewables offer 12 chances to miss a dose!

Is ProHeart 12 right for your dog?

With ProHeart 12, you can ensure your best friend is protected year-round

In clinical trials, ProHeart 12 was 100% effective against heartworm disease* in dogs.¹

In 6 studies, ProHeart 12 demonstrated safety for:

- Pregnant dogs and their puppies
- Dogs sensitive to ivermectin—an ingredient found in monthly heartworm products

ProHeart 12⁺ has been trusted by Australian veterinarians for over 19 years.

*Dirofilaria immitis. ¹In 3 well-controlled studies. ²Known as ProHeart SR-12 in Australia.

Consider which heartworm prevention option is best for your dog.

One ProHeart 12 injection can easily fit in with your dog’s annual wellness visit. Ask your veterinarian!
**IMPORTANT SAFETY INFORMATION:** Use 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 12 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. The most common reported side effects in clinical trials were vomiting, lethargy, diarrhea, and anorexia. People should avoid inhalation, contact with eyes, or accidental self-injection. Certification is required before veterinarians and staff administer PROHEART 12. See full Prescribing Information in pocket.

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% glycercyl 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 heartworm (Ancylostoma caninum and Uncinaria stenocephala) infections.

DOSE 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 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 mosquitos. 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

<table>
<thead>
<tr>
<th>Pounds (lb)</th>
<th>Kilograms (kg)</th>
<th>Dose Volume* mL/Dog</th>
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<tbody>
<tr>
<td>11</td>
<td>5</td>
<td>0.25</td>
</tr>
<tr>
<td>22</td>
<td>10</td>
<td>0.50</td>
</tr>
<tr>
<td>33</td>
<td>15</td>
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<tr>
<td>44</td>
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<td>55</td>
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<tr>
<td>121</td>
<td>55</td>
<td>2.75</td>
</tr>
<tr>
<td>132</td>
<td>60</td>
<td>3.00</td>
</tr>
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</table>

*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 gently before 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 a 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 to dogs in cases of 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 O. immitis microfilariae.

Caution should be used when administering ProHeart 12 to heartworm positive dogs (see ADVERSE REACTIONS).
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, hypproteinemia, 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 similarly 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 http://www.fda.gov/AnimalVeterinary/SafetyHealth.

INFORMATION FOR DOG OWNERS

Always provide the 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 cyanogenes subspecies noncyanogenicus. Moxidectin is a pentacyclic 16-membered lactone macroclide.

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 larval 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 group), 1.5 mg/kg body weight (3X group), or 2.5 mg/kg body weight (5X group). 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-injection (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:

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

Constitution of the 10 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 8 mL of the unique sterile vehicle from the vial.

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.

6. Discard unused sterile vehicle and needles.

7. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.

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.

10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. Dose promptly after drawing into dosing syringe.

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

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