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 (Ankylostoma 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 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 1 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>
<thead>
<tr>
<th>Dog Weight</th>
<th>Dose Volume*</th>
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</thead>
<tbody>
<tr>
<td>Pounds (lb)</td>
<td>Kilograms (kg)</td>
</tr>
<tr>
<td>11 lb</td>
<td>5 kg</td>
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<tr>
<td>22 lb</td>
<td>10 kg</td>
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<tr>
<td>33 lb</td>
<td>15 kg</td>
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<tr>
<td>44 lb</td>
<td>20 kg</td>
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<tr>
<td>55 lb</td>
<td>25 kg</td>
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<tr>
<td>66 lb</td>
<td>30 kg</td>
</tr>
<tr>
<td>77 lb</td>
<td>35 kg</td>
</tr>
<tr>
<td>88 lb</td>
<td>40 kg</td>
</tr>
<tr>
<td>99 lb</td>
<td>45 kg</td>
</tr>
<tr>
<td>110 lb</td>
<td>50 kg</td>
</tr>
<tr>
<td>121 lb</td>
<td>55 kg</td>
</tr>
<tr>
<td>132 lb</td>
<td>60 kg</td>
</tr>
</tbody>
</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 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® 6 and ProHeart® 12 are available in the same formulation, but ProHeart® 12 is three times the concentration of ProHeart® 6. Not all adverse reactions are reported to FDA/CVMA. 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 weight in dogs given ProHeart® 12. ProHeart® 12 is contraindicated in animals previously found to be hypersensitive to this drug or ProHeart® 6.

Humoral Adverse Reactions
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 heartworms.

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 drug reactions were recorded.

Table 1: Number of Dogs* with Adverse Reactions Reported During the ProHeart® 12 Field Study

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

*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 in 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 reported on post-approval adverse drug reaction forms. Two ProHeart® 6 (moxidectin) treated dogs experienced anaphylactoid reactions within 24 hours of administration. One dog was pre-treated with 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 in the first 24 hours. The dog was withdrawn from the study prior to the second monthly dose.

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.
Immune: anaphylaxis and/or anaphylactoid reactions, urticaria, head/face 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, hypoprothrombinemia, hyperbilirubinemia, hepatitis

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 http://www.fda.gov/AnimalVeterinary/SafetyHealth.

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 cyanogriseus 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. stenocephalum, are susceptible.

Following infection 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. stenocephalum. 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 inoculated 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:
- 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.

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. The product may appear as a hazy to milky 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.

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.

<table>
<thead>
<tr>
<th>1-Pack</th>
<th>5-Pack</th>
<th>10-Pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 10% moxidectin sterile microspheres- 889 mg/vial</td>
<td>S - 10% moxidectin sterile microspheres- 889 mg/vial</td>
<td>10 - 10% moxidectin sterile microspheres- 889 mg/vial</td>
</tr>
<tr>
<td>1 - Sterile vehicle- 8 mL/vial</td>
<td>5 - Sterile vehicle- 8 mL/vial</td>
<td>10 - Sterile vehicle- 8 mL/vial</td>
</tr>
</tbody>
</table>

Approved by FDA under NADA #: 141-519

Revised: April 2019

Distributed by: Zoetis Inc., Kalamazoo, MI 49007

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