Simparica (sarolaner) Chewables
ProHeart 12 (moxidectin)
PROVEN PROTECTION

ZOETIS PETCARE

Protecting Your Pharmacy

Simparica & ProHeart 12 help keep parasiticide purchases in your pharmacy.

With **Simparica,** dog owners don't have to buy tick & flea protection elsewhere—affordable pricing helps you compete with retail brands.

With **ProHeart 12,** you can offer heartworm disease prevention as a vet-administered service right in your practice.

Boost Revenue

Add more value for your clients

Affordable pricing
Simparica helps ensure tick and flea **sales stay in your practice.**

Annual prevention ensured
Offer your clients vet-administered **ProHeart 12** as a heartworm disease prevention service—1 year of protection with just 1 injection.

Zoetis Petcare Rewards
When clients protect their dogs with **Simparica** and **ProHeart 12,** they can earn **up to $55 they can use in your practice.**

Improving Compliance

80% of pet owners have missed at least 1 dose of tick & flea prevention[1]

66% of dog owners† left veterinary clinics without any heartworm disease prevention[2]

Consistent **35-day tick & flea protection** from a monthly dose of **Simparica** and **1 full year of heartworm disease* protection** from yearly **ProHeart 12** can help pet owners worry less about late or missed doses.

*Caused by *Dirofilaria Immitis.* †National average.
1. 2019 Zoetis Survey. Wakefield Research.
2. VetStreet Data Analytics 2017. BIAHP350 Parasiticide purchases for 2017. Data on file. Zoetis Inc.

IMPORTANT SAFETY INFORMATION: Simparica is for use only in dogs, 6 months of age and older. Simparica may cause abnormal neurologic signs such as tremors, unsteadiness, and/or seizures. Simparica has not been evaluated in dogs that are pregnant, breeding or lactating. Simparica has been safely used in dogs treated with commonly prescribed vaccines, parasiticides and other medications. The most frequently reported adverse reactions were vomiting and diarrhea. See full **Prescribing Information**.

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**.

Simparica®
(sarolaner) Chewables

FOR ORAL USE IN DOGS ONLY

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

Description:
SIMPARICA is a flavored, chewable tablet for administration to dogs over 6 months of age according to their weight. Each tablet is formulated to provide a minimum sarolaner dosage of 0.91 mg/lb (2 mg/kg) body weight.
Sarolaner is a member of the isoxazoline class of parasiticides and the chemical name is 1-(5'-((5S)-5-(3,5-Dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-3'-H-spiro(azetidine-3,1'-(2) benzofuran)-1-yl)-2-(methylsulfonyl)ethanone. SIMPARICA contains the S-enantiomer of sarolaner.

Indications:
SIMPARICA kills adult fleas, and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of tick infestations [*Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or greater.

Dosage and Administration:
SIMPARICA is given orally once a month at the recommended minimum dosage of 0.91 mg/lb (2 mg/kg).

Dosage Schedule:

Body Weight	SAROLANER per Tablet (mg)	Number of Tablets Administered
2.8 to 5.5 lbs	5	One
5.6 to 11.0 lbs	10	One
11.1 to 22.0 lbs	20	One
22.1 to 44.0 lbs	40	One
44.1 to 88.0 lbs	80	One
88.1 to 132.0 lbs	120	One
>132.1 lbs	Administer the appropriate combination of tablets	

SIMPARICA can be offered by hand, in the food, or administered like other tablet medications.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If a dose is missed, administer SIMPARICA and resume a monthly dosing schedule.

SIMPARICA should be administered at monthly intervals.

Flea Treatment and Prevention:
Treatment with SIMPARICA may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with SIMPARICA can continue the entire year without interruption.

To minimize the likelihood of flea re-infestation, it is important to treat all dogs and cats within a household with an approved flea control product.

Tick Treatment and Control:
Treatment with SIMPARICA can begin at any time of the year (see **Effectiveness**).

Contraindications:
There are no known contraindications for the use of SIMPARICA.

Warnings:
Not for use in humans. Keep this and all drugs out of reach of children. For use in dogs only. Do not use SIMPARICA in cats.

SIMPARICA should not be used in dogs less than 6 months of age (see **Animal Safety**).

Keep SIMPARICA in a secure location out of reach of dogs, cats and other animals to prevent accidental ingestion or overdose.

Precautions:
Sarolaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.

The safe use of SIMPARICA has not been evaluated in breeding, pregnant, or lactating dogs.

Adverse Reactions:
SIMPARICA was administered in a well-controlled US field study, which included a total of 479 dogs (315 dogs treated with SIMPARICA and 164 dogs treated with active control once monthly for three treatments).

Over the 90-day study period, all observations of potential adverse reactions were recorded.

Table 1. Dogs with adverse reactions

Adverse reaction	sarolaner	sarolaner	active control	active control
	N	% (n = 315)	N	% (n =164)
Vomiting	3	0.95%	9	5.50%
Diarrhea	2	0.63%	2	1.20%
Lethargy	1	0.32%	2	1.20%
Inappetence	0	0%	3	1.80%

Additionally, one female dog aged 8.6 years exhibited lethargy, ataxia while posturing to eliminate, elevated third eyelids, and inappetence one day after receiving SIMPARICA concurrently with a heartworm preventative (ivermectin/pyrantel pamoate). The signs resolved one day later. After the day 14 visit, the owner elected to withdraw the dog from the study.

Abnormal neurologic signs such as tremors, decreased conscious proprioception, ataxia, decreased or absent menace, and/or seizures were reported in dogs receiving SIMPARICA (see **Animal Safety**).

Post Approval Experience (2019):
The following adverse events are based on post-approval adverse drug experience reporting for SIMPARICA. Not all adverse events 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 reported for dogs are listed in decreasing order of reporting frequency: Vomiting, tremors, lethargy, seizure, diarrhea (with and without blood), anorexia, ataxia, pruritus, hypersalivation and hyperactivity.

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

Clinical Pharmacology:
Sarolaner is rapidly and well absorbed following oral administration of SIMPARICA. In a study of 12 Beagle dogs the mean maximum plasma concentration (C_{max}) was 1100 ng/mL and the mean time to maximum concentration (T_{max}) occurred at 3 hours following a single oral dose of 2 mg/kg to fasted animals. The mean oral bioavailability was 86% and 107% in fasted and fed dogs, respectively. The mean oral $T_{1/2}$ values for fasted and fed animals was 10 and 12 days respectively.

Sarolaner is distributed widely; the mean volume of distribution (Vdss) was 2.81 L/kg bodyweight following a 2 mg/kg intravenous dose of sarolaner. Sarolaner is highly bound (≥99.9%) to plasma proteins. The metabolism of sarolaner appears to be minimal in the dog. The primary route of sarolaner elimination from dogs is biliary excretion with elimination via the feces.

Following repeat administration of SIMPARICA once every 28 days for 10 doses to Beagle dogs at 1X, 3X, and 5X the maximum intended clinical dose of 4 mg/kg, steady-state plasma concentrations were reached after the 6th dose. Following treatment at 1X, 3X, and 5X the maximum intended clinical dose of 4 mg/kg, sarolaner systemic exposure was dose proportional over the range 1X to 5X.

Mode of Action:
The active substance of SIMPARICA, sarolaner, is an acaricide and insecticide belonging to the isoxazoline group. Sarolaner inhibits the function of the neurotransmitter gamma aminobutyric acid (GABA) receptor and glutamate receptor, and works at the neuromuscular junction in insects. This results in uncontrolled neuromuscular activity leading to death in insects or acarines.

Effectiveness:
In a well-controlled laboratory study, SIMPARICA began to kill fleas 3 hours after initial administration and reduced the number of live fleas by ≥96.2% within 8 hours after flea infestation through Day 35.

In a separate well-controlled laboratory study, SIMPARICA demonstrated 100% effectiveness against adult fleas within 24 hours following treatment and maintained 100% effectiveness against weekly re-infestations for 35 days.

In a study to explore flea egg production and viability, SIMPARICA killed fleas before they could lay eggs for 35 days. In a study to simulate a flea-infested home environment, with flea infestations established prior to the start of treatment and re-infestations on Days 7, 37 and 67, SIMPARICA administered monthly for three months demonstrated >95.6% reduction in adult fleas within 14 days after treatment and reached 100% on Day 60.

In well-controlled laboratory studies, SIMPARICA demonstrated ≥99% effectiveness against an initial infestation of *Amblyomma americanum, Amblyomma maculatum, Dermacentor variabilis, Ixodes scapularis,* and *Rhipicephalus sanguineus* 48 hours post-administration and maintained >96% effectiveness 48 hours post re-infestation for 30 days.

In a well-controlled 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of SIMPARICA against fleas on Day 30, 60 and 90 visits compared to baseline was 99.4%, 99.8%, and 100%, respectively. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis and pruritus as a direct result of eliminating fleas.

Animal Safety:
In a margin of safety study, SIMPARICA was administered orally to 8-week-old Beagle puppies at doses of 0, 1X, 3X, and 5X the maximum recommended dose (4 mg/kg) at 28-day intervals for 10 doses (8 dogs per group). The control group received placebo tablets. No neurologic signs were observed in the 1X group. In the 3X group, one male dog exhibited tremors and ataxia post-dose on Day 0; one female dog exhibited tremors on Days 1, 2, 3, and 5; and one female dog exhibited tremors on Day 1. In the 5X group, one female dog had a seizure on Day 61 (5 days after third dose); one female dog had tremors post-dose on Day 0 and abnormal head coordination after dosing on Day 140; and one female dog exhibited seizures associated with the second and fourth doses and tremors associated with the second and third doses. All dogs recovered without treatment. Except for the observation of abnormal head coordination in one dog in the 5X group two hours after dosing on Day 140 (dose 6). There were no treatment-related neurological signs observed once the dogs reached the age of 6 months.

In a separate exploratory pharmacokinetic study, one female dog dosed at 12 mg/kg (3X the maximum recommended dose) exhibited lethargy, anorexia, and multiple neurological signs including ataxia, tremors, disorientation, hypersalivation, diminished proprioception, and absent menace, approximately 2 days after a third monthly dose. The dog was not treated, and was ultimately euthanized. The first two doses resulted in plasma concentrations that were consistent with those of the other dogs in the treatment group. Starting at 7 hours after the third dose, there was a rapid 2.5 fold increase in plasma concentrations within 41 hours, resulting in a C_{max} more than 7-fold higher than the mean C_{max} at the maximum recommended use dose. No cause for the sudden increase in sarolaner plasma concentrations was identified.

Storage Information:
Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:
SIMPARICA (sarolaner) Chewables are available in six flavored tablet sizes: 5, 10, 20, 40, 80, and 120 mg. Each tablet size is available in color-coded packages of one, three, or six tablets.

Approved by FDA under NADA # 141-452

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: June 2019

50070902A&P

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 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 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:

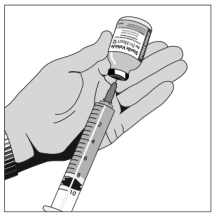
Females: A reproductive laboratory study in 40 female Beagle dogs assessed the safety of ProHeart 12 at a single 1.5 mg/kg body weight (3X) dose. The dogs were divided into four treatment groups of 8 dogs per group to cover the critical periods of the reproductive cycle (pre-mating, mating, mid-gestation, 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.

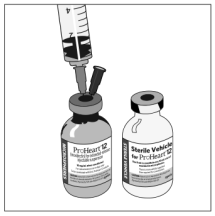
Males: A reproductive laboratory study assessed the safety of ProHeart 12 in eight male Beagle dogs at a single 1.5 mg/kg body weight (3X) dose. The control group (8 dogs) received a saline injection. No adverse reactions were noted in any of the dogs during the 91-day study. No clinically significant 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:

- 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.
   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

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