Simparica TRIO® (sarolaner, moxidectin, and pyrantel chewable tablets)

Simparica® (sarolaner) Chewables

Simparica Trio and Simparica Satisfaction Guarantee

If you or your clients feel that Simparica Trio® (sarolaner, moxidectin, and pyrantel chewable tablets) or Simparica® (sarolaner) Chewables isn't providing sufficient protection, please call our medical support team to discuss our Satisfaction Guarantee. We will work with you to ensure that you and your clients are satisfied with the performance of Simparica Trio or Simparica or we will refund the cost of your purchase.*

The Simparica Trio and Simparica Satisfaction Guarantee is available to any individual who has purchased Simparica Trio or Simparica from a veterinarian or via a veterinarian's prescription from a Zoetis approved online distributor.**

HEARTWORM DISEASE GUIDELINES (SIMPARICA TRIO ONLY):

If any dog determined by a licensed veterinarian to be free of heartworm infection at the onset of treatment with Simparica Trio develops heartworm disease, we will provide reimbursement (up to $1,000 and provide Diroban® (melarsomine dihydrochloride) or provide reasonable acquisition costs of melarsomine dihydrochloride) associated with the diagnosis and treatment of heartworm disease and provide a year's supply of Simparica Trio or ProHeart® 6 (moxidectin) or ProHeart® 12 (moxidectin).

Canine Heartworm Reimbursement Requirements:

- Simparica Trio was used, at all times, according to its label directions.
- Confirmation of heartworm-positive status by two separate blood samples using at least two different brands of antigen tests are required to document heartworm positive status.
  - The use of an antigen test will be the standard for determining heartworm status.
  - Knott's or any filter test for the detection of microfilariae is not sufficient evidence for pretreatment heartworm negative status.
- Dogs previously treated for heartworm disease must have a negative antigen test prior to starting Simparica Trio.
- Dogs starting or changing heartworm preventatives are required to have two negative antigen tests at least 6 months apart after initiation of Simparica Trio treatment.†

TICK GUIDELINES (SIMPARICA TRIO AND SIMPARICA):

Simparica Trio and Simparica are indicated for the prevention of *Borrelia burgdorferi* infections, the causative agent of Lyme disease, as a direct result of killing *Ixodes scapularis* vector ticks. We will reimburse you up to $30.00 for an approved alternative tick treatment for dogs, or reimburse you the cost of one dose of Simparica Trio or Simparica. This Satisfaction Guarantee does not cover any other costs, including, but not limited to, those associated with the control of tick infestations in or around living quarters, or medical treatments or procedures.

Lyme Satisfaction Guarantee:

Zoetis will cover reasonable diagnostic and treatment costs for suspected cases of canine Lyme disease for qualifying patients. Coverage begins one month after a negative Lyme test* and administration of Simparica Trio or Simparica according to label directions. If diagnostic tests confirm exposure to *Borrelia burgdorferi* and the dog is showing clinical signs, this Satisfaction Guarantee will cover physical examination, ancillary diagnostic and therapeutic charges up to a maximum of $2,500.

Qualifying Patients:

1. The owner must show proof of the dog's negative Lyme test within 1 month of starting treatment with Simparica Trio or Simparica and have a negative yearly test thereafter. Any qualitative antibody test for Lyme disease may be used as a screening tool to detect natural exposure to *Borrelia burgdorferi*. Examples include: Zoetis VetScan® Lyme Rapid Test, IDEXX SNAP® 3Dx® Test or SNAP® 4Dx® Test and ANTECH Diagnostics® AccuPlex™4 Test.
2. Client must be able to demonstrate that they purchased enough doses of Simparica Trio or Simparica to provide continuous protection to their dog from the date of the negative Lyme test through the date of the claim.
3. To qualify for additional benefits from the Zoetis Immunization Support Guarantee, the client must show that: (a) their dog is appropriately vaccinated for Lyme disease; (b) the most recent Lyme vaccine was administered in the preceding 12 months; and (c) the most recent Lyme vaccine was a Zoetis Lyme vaccine (Vanguard® crLyme or Lymevax®). If the dog is diagnosed with Lyme disease, Zoetis will reimburse diagnostic and treatment costs up to $7,500 if the patient has received continuous protection with Simparica Trio or Simparica, according to label directions, was vaccinated appropriately AND the last dose of Lyme vaccine administered was a Zoetis vaccine.

Simparica TRIO
(sarolaner, moxidectin, and pyrantel chewable tablets)

Simparica
(sarolaner) Chewables

Simparica Trio and Simparica Satisfaction Guarantee

FLEA GUIDELINES (SIMPARICA TRIO AND SIMPARICA):

Simparica Trio and Simparica kills adult fleas, and treats and prevents flea infestations. The affected dog must have been on Simparica Trio or Simparica for a minimum of 30 days prior to the report. All other pets in the home must also be treated with a flea control product for a minimum of 30 days prior to the report. We will reimburse you up to $30.00 for an alternative approved flea treatment or reimburse you the cost of one dose of Simparica Trio or Simparica. The Satisfaction Guarantee does not cover any other costs, including, but not limited to, those associated with the control of flea infestations in and around living quarters, or medical treatments or procedures.

HOOKWORM, ROUNDWORM, WHIPWORM, TAPEWORM GUIDELINES (SIMPARICA TRIO ONLY):

Simparica Trio treats and controls roundworm (immature and adult *Toxocara canis* and adult *Toxascaris leonina*) and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections. If you are dispensing Simparica Trio and the dog is found to be positive with roundworms or hookworms demonstrated in the fecal sample, we will provide reimbursement for the reasonable costs up to $100 for an approved treatment.

Simparica Trio has not demonstrated efficacy against whipworms or tapeworms in dogs or puppies. However, if you are dispensing Simparica Trio to a dog or puppy and such dog or puppy is found to be positive with tapeworms demonstrated in the fecal sample, we will provide you Cestex (epsiprantel) free of charge. If a dog is positive with whipworms, we will provide reimbursement for the reasonable costs up to $100 for an approved treatment.

SIMPARICA TRIO IMPORTANT SAFETY INFORMATION: Use with caution in dogs with a history of seizures. Simparica Trio contains sarolaner, a member of the isoxazoline class, which has been associated with neurologic adverse reactions including tremors, ataxia, and seizures in dogs with or without a history of neurologic disorders. The safe use of Simparica Trio has not been evaluated in breeding, pregnant, or lactating dogs. The most frequently reported adverse reactions in clinical trials were vomiting and diarrhea. See full Prescribing Information, attached.

SIMPARICA IMPORTANT SAFETY INFORMATION: Simparica is for use only in dogs 6 months of age and older. Simparica may cause neurologic signs such as tremors, unsteadiness and/or seizures in dogs with or without a history of neurologic disorders. Simparica has not been evaluated in pregnant, breeding or lactating dogs. The most common adverse reactions in clinical trials were vomiting and diarrhea. See full Prescribing Information, attached.

Zoetis reserves the right to modify or discontinue this program at any time for any reason. Call Zoetis Veterinary Medical Information & Product Support with Satisfaction Guarantee questions at 1-888-ZOETIS1.

** Subject to program requirements outlined in this document.*

*** Guarantee applies to current products purchased from a veterinarian or from a pharmacy through fulfillment of a valid veterinary prescription. Simparica Trio or Simparica obtained free of charge is not eligible. All claims via distribution must be accompanied by a valid proof of purchase.*

† Dogs that have not previously received heartworm prevention, or those that have received inconsistent heartworm prevention, prior to starting Simparica Trio 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."

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Simparica TRIO®

(sarolaner, moxidectin, and pyrantel chewable tablets)

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 TRIO (sarolaner, moxidectin, and pyrantel chewable tablets) is a flavored, chewable tablet for administration to dogs 8 weeks of age and older. Each tablet is formulated to provide minimum dosages of 0.54 mg/lb (1.2 mg/kg) sarolaner, 0.011 mg/lb (24 µg/kg) moxidectin, and 2.27 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

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 TRIO contains the S-enantiomer of sarolaner.

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. The chemical name for moxidectin is (6R,23E,25S)-5-O-Demethyl-28-deoxy-25-[(1E)-1,3-dimethyl-1-buten-1-yl]-6,28-epoxy-23-(methoxyimino)milbemycin B.

Pyrantel belongs to a family classified chemically as tetrahydropyrimidines and the chemical name is (E)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl) vinyl] pyrimidine 4,4' methylenebis [3-hydroxy-2-naphthoate](1:1). It is a yellow, water-insoluble crystalline salt of the tetrahydropyrimidine base and pamoic acid containing 34.7% base activity.

INDICATIONS
SIMPARICA TRIO is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and hookworm (L4, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*) infections. SIMPARICA TRIO kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, and the treatment and control of tick infestations with *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 and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater. SIMPARICA TRIO is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

DOSAGE AND ADMINISTRATION
SIMPARICA TRIO is given orally once a month, at the recommended minimum dose of 0.54 mg/lb (1.2 mg/kg) sarolaner, 0.011 mg/lb (24 µg/kg) moxidectin, and 2.27 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

Dosage Schedule

Body Weight (lbs)	Sarolaner per Tablet (mg)	Moxidectin per Tablet (mg)	Pyrantel per Tablet (mg)	Number of Tablets Administered
2.8 to 5.5	3	0.06	12.5	One
5.6 to 11.0	6	0.12	25	One
11.1 to 22.0	12	0.24	50	One
22.1 to 44.0	24	0.48	100	One
44.1 to 88.0	48	0.96	200	One
88.1 to 132.0	72	1.44	300	One
>132.0	Administer the appropriate combination of tablets			

SIMPARICA TRIO can be offered to the dog with or without food.

Care should be taken to ensure that the dog consumes the complete dose and that part of the dose is not lost or refused. If a dose is missed, give SIMPARICA TRIO immediately and resume monthly dosing.

Heartworm Prevention:
SIMPARICA TRIO should be administered at monthly intervals year-round or at least within one month of the animal's first seasonal exposure to mosquitoes and continuing until at least 1 month after the dog's last seasonal exposure. If a dose is missed, give SIMPARICA TRIO immediately and resume monthly dosing. When replacing a monthly heartworm preventive product, SIMPARICA TRIO should be given within one month of the last dose of the former medication.

Flea Treatment and Prevention:
Treatment with SIMPARICA TRIO may begin at any time of the year. SIMPARICA TRIO should be administered year-round at monthly intervals or started at least one month before fleas become active.

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

Tick Treatment and Control:
Treatment with SIMPARICA TRIO can begin at any time of the year. SIMPARICA TRIO should be administered year-round at monthly intervals or started at least one month before ticks become active.

Intestinal Nematode Treatment and Control:
For the treatment of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and hookworm (L4, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*) infections, SIMPARICA TRIO should be administered once as a single dose. Monthly use of SIMPARICA TRIO will control any subsequent infections.

CONTRAINDICATIONS
There are no known contraindications for the use of SIMPARICA TRIO.

WARNINGS
Not for use in humans. Keep this and all drugs out of reach of children.

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

PRECAUTIONS
Sarolaner, one of the ingredients in SIMPARICA TRIO, 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.

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

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

ADVERSE REACTIONS
In a field safety and effectiveness study, SIMPARICA TRIO was administered to dogs for the prevention of heartworm disease. The study included a total of 410 dogs treated once monthly for 11 treatments (272 treated with SIMPARICA TRIO and 138 treated with an active control). Over the 330-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported in the SIMPARICA TRIO group are presented in the following table.

Table 1. Dogs with Adverse Reactions

Clinical Sign	SIMPARICA TRIO *n* = 272	Active Control *n* = 138
Vomiting	14.3%	10.9%
Diarrhea	13.2%	8.0%
Lethargy	8.5%	6.5%
Anorexia	5.1%	5.8%
Polyuria	3.7%	3.6%
Hyperactivity	2.2%	0.7%
Polydipsia	2.2%	2.9%

In a second field safety and effectiveness study, SIMPARICA TRIO was administered to 278 dogs with fleas. Adverse reactions in dogs treated with SIMPARICA TRIO included diarrhea.

In a third field safety and effectiveness study, SIMPARICA TRIO was administered to 120 dogs with roundworms. Adverse reactions in dogs treated with SIMPARICA TRIO included diarrhea and vomiting.

CONTACT INFORMATION
For a copy of the Safety Data Sheet or to report adverse reactions, call Zoetis Inc. 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.

CLINICAL PHARMACOLOGY
Following oral administration of SIMPARICA TRIO in Beagle dogs (13 to 15 months of age at the time of initial dosing), sarolaner and moxidectin were rapidly and well-absorbed. Following a single oral dose of SIMPARICA TRIO (sarolaner dose of 1.2 mg/kg), the sarolaner mean maximum plasma concentration (C_{max}) was 523 ng/mL with a mean time to maximum concentration (T_{max}) of 3.5 hours and an absolute bioavailability of 88%. At a moxidectin dose of 0.024 mg/kg, the moxidectin mean C_{max} was 13.1 ng/mL with a mean T_{max} of 2.4 hours and an absolute bioavailability of 67%.

Following intravenous (IV) dosing of a combination solution of sarolaner and moxidectin, the sarolaner volume of distribution (V_{ss}) was 2.4 L/kg and systemic clearance (CL) was 6.0 mL/kg/hr. For moxidectin the V_{ss} was 7.65 L/kg and CL was 26.6 mL/kg/hr. The terminal half-lives were similar after oral and IV dosing for both sarolaner (12 days) and moxidectin (11 days). The primary route of elimination of both sarolaner and moxidectin is biliary excretion with minimal metabolism.

Following an oral dose of SIMPARICA TRIO containing 5 mg/kg pyrantel (as pamoate salt), pyrantel has measurable plasma concentrations, but they are low and highly variable. Pyrantel pamoate is intended to remain in the gastrointestinal tract allowing for delivery of effective concentrations to gastrointestinal nematodes.

MODE OF ACTION
SIMPARICA TRIO contains three active pharmaceutical ingredients, sarolaner, moxidectin, and pyrantel pamoate.

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.

Moxidectin is an endectocide in the macrocyclic lactone class. Moxidectin acts by interfering with the chloride channel-mediated neurotransmission in the parasite. This results in paralysis and death of the parasite.

Pyrantel pamoate is a nematocide belonging to the tetrahydropyrimidine class. Pyrantel acts as a depolarizing, neuromuscular-blocking agent in susceptible parasites, which causes paralysis and death or expulsion of the organism.

EFFECTIVENESS
Heartworm Prevention
In two well-controlled laboratory studies, a single oral dose of SIMPARICA TRIO was 100% effective in preventing the development of adult *D. immitis* in dogs inoculated with infective larvae 30 days before treatment.

In a well-controlled US field study consisting of 246 dogs administered SIMPARICA TRIO and 119 administered an active control, no dogs treated with SIMPARICA TRIO tested positive for heartworm disease. All dogs treated with SIMPARICA TRIO were negative for *D. immitis* antigen and blood microfilariae at study completion on day 330.

Flea Treatment and Prevention
In a well-controlled laboratory study, SIMPARICA TRIO began to kill fleas at 4 hours and demonstrated 100% effectiveness at 8 hours after initial administration. After weekly re-infestations, SIMPARICA TRIO reduced the number of live fleas by ≥97.8% within 12 hours of infestation for 28 days.

In a separate well-controlled laboratory study, SIMPARICA TRIO demonstrated 100% effectiveness against adult fleas within 24 hours following treatment and maintained ≥99.7% effectiveness against weekly re-infestations for 35 days.

In a study to explore flea egg production and viability, SIMPARICA TRIO killed fleas before they could lay eggs for 35 days.

In a well-controlled 60-day US field study conducted in dogs with existing flea infestations of varying severity, the effectiveness of SIMPARICA TRIO against fleas on Day 30 and 60 visits was 99.0% and 99.7%, respectively, compared to baseline. 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.

Tick Treatment and Control
In a well-controlled laboratory study, SIMPARICA TRIO began to kill existing *I. scapularis* within 8 hours, SIMPARICA TRIO reduced the number of live ticks by ≥94.2% within 24 hours of infestation for 28 days.

In well-controlled laboratory studies, SIMPARICA TRIO demonstrated ≥98.9% effectiveness against an existing infestation of *Amblyomma maculatum*, *Ixodes scapularis*, *Rhipicephalus sanguineus*, and *Dermacentor variabilis* 48 hours post-administration and maintained ≥90.4% effectiveness 48 hours after re-infestation for at least 28 days. Against *Amblyomma americanum*, SIMPARICA TRIO demonstrated ≥99.4% effectiveness 72 hours after treatment of existing infestations, and maintained ≥98.4% effectiveness 72 hours after re-infestation for at least 28 days. In two separate, well-controlled laboratory studies, SIMPARICA TRIO was effective at preventing *Borrelia burgdorferi* infections after dogs were infested with *Ixodes scapularis* vector ticks 28 days post-treatment.

Intestinal Nematode Treatment and Control
Elimination of roundworms (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and hookworm (L4, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*) was demonstrated in well-controlled laboratory studies.

In a 10-day multi-center field study, SIMPARICA TRIO was effective against *Toxocara canis* and reduced fecal egg counts 99.2%.

ANIMAL SAFETY
Margin of Safety: SIMPARICA TRIO was administered orally to 8-week-old Beagle puppies at doses of 1, 3, and 5X the maximum labeled dose (2.4 mg/kg sarolaner, 48 µg/kg moxidectin, and 10 mg/kg pyrantel) at 28 day intervals for 7 treatments. Dogs in the control group received placebo. There were no clinically-relevant, treatment related effects on clinical observations, body weights, food consumption, clinical pathology (hematology, coagulation, serum chemistry, and urinalysis), gross pathology, histopathology, or organ weights. During the end-of-study ophthalmic examination, the following change was found: one 1X dog had retinal dysplasia (OS folds).

Ivermectin-sensitive Collie Safety:
SIMPARICA TRIO was administered orally once at 1, 3 and 5X the maximum labeled dose to Collies that had been pre-screened for avermectin sensitivity. Dogs in the control group received placebo. Clinical signs (ataxia, muscle fasciculations, mydriasis) associated with avermectin sensitivity were observed in the 5X group. All dogs were completely recovered by the third day of the study.

Heartworm-Positive Safety:
SIMPARICA TRIO was administered orally at 1 and 3X the maximum labeled dose at 28 day intervals for 3 treatments to Beagle dogs with patent adult heartworm infections and circulating microfilariae. Dogs in the control group received placebo. Diarrhea occurred more commonly in the treated dogs and also more often in the 3X group compared with the 1X group. Two dogs (1 each in 1X and 3X) developed a fever less than 24 hours after the first dose. The fever may have been a transient reaction to a rapid microfilaria reduction. Both dogs recovered without treatment.

Field Safety: In three well-controlled field studies, SIMPARICA TRIO was used concurrently with other medications such as vaccines, antimicrobials, anthelmintics, antiprotozoals, steroidal and non-steroidal anti-inflammatory agents, anesthetic agents and analgesics. No adverse reactions were associated with the concurrent use of SIMPARICA TRIO and other medications.

STORAGE CONDITIONS
Store at or below 30°C (86°F).

HOW SUPPLIED
SIMPARICA TRIO is available in six flavored tablet sizes (see **DOSAGE AND ADMINISTRATION**). Each tablet size is available in packages of one, three, or six tablets.

Approved by FDA under NADA # 141-521

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Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: July 2021

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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. SIMPARICA is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

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 two separate, well-controlled laboratory studies, SIMPARICA was effective at preventing *Borrelia burgdorferi* infections after dogs were infested with *Ixodes scapularis* vector ticks 28 days post-treatment.

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.

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