Simparica® (sarolaner) Chewables **Dogged Protection**

Simparica Satisfaction Guarantee

If you or your clients feel that Simparica™ (sarolaner) Chewables aren't providing sufficient flea and tick 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 or we will refund the cost of your purchase.*

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

FLEA GUIDELINES

Simparica kills adult fleas, and treats and prevents flea infestations (*Ctenocephalides felis*) for one month in dogs 6 months of age and older, weighing 2.8 pounds or more. The affected dog must be on 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 additional dose of Simparica. The Satisfaction Guarantee does not cover any other costs, including, but not limited to, those associated with the the control of flea infestations in and around living quarters, or medical treatments or procedures.

TICK GUIDELINES

Simparica treats and controls tick infestations from *Ixodes scapularis* (black-legged "deer" tick), *Amblyomma americanum* (Lone Star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick). We will reimburse you up to $30.00 for an approved alternative tick treatment for dogs, or reimburse you the cost of one additional dose of 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 according to label directions. If the diagnostics confirm exposure to *Borrelia burgdorferi* and the dog is showing clinical signs, the Simparica 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 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: IDEXX SNAP® 3Dx® Test or SNAP® 4Dx® Test, ANTECH Diagnostics® AccuPlex™4 Test, and Abaxis™ VetScan™ Lyme Rapid Test.
2. Client must be able to demonstrate that they purchased enough doses of Simparica to provide continuous protection to their dog from the date of the negative Lyme test through the date of the claim. The Companion Animal Parasite Council (CAPC) recommends year-round flea and tick protection.
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 used according to label directions, was vaccinated appropriately AND the last dose of Lyme vaccine administered was a Zoetis vaccine.

* 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 obtained free of charge is not eligible. All claims via distribution must be accompanied by a valid proof of purchase.

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

ZOETIS PETCARE

Simparica® (sarolaner) Chewables **Dogged Protection**

Kills deer ticks fast

In a study, Simparica blocked the transmission of Lyme from *Ixodes scapularis* (Black-legged "deer" tick)[1]

- Demonstrated 98.8% efficacy against existing infestations just 12 hours after treatment.[2]
  - Lyme is typically transmitted within 24 to 48 hours.
- Maintained a rapid speed of kill throughout the month.

In a study, Simparica blocked transmission of *Borrelia burgdorferi*[1]

The study looked at 2 groups of dogs:

1. Control dogs treated with placebo chewable
2. Simparica dogs treated at label dose

After 4 full weeks (28 days), all dogs were infested with *Borrelia burgdorferi*-infected ticks.
All dogs were tested for Lyme using the SNAP® 4Dx® test and Lyme spirochete using PCR tests and culturing. Blood samples were collected from each dog in approximately 2 week intervals ending almost 10 weeks (76 days) after tick infestation.

Even when challenged near the end of the treatment period, Simparica prevented the transmission of Lyme disease.

LYME DISEASE Presence of *Borrelia burgdorferi*	Simparica® (sarolaner) Chewables	PLACEBO
Antibody Test SNAP® 4Dx®	**All Simparica** Dogs tested **NEGATIVE!**	**6 out of 8** dogs were **POSITIVE**
PCR and Culture	**All Simparica** Dogs tested **NEGATIVE!**	**7 out of 8** dogs were **POSITIVE**

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, decreased conscious proprioception, ataxia, decreased or absent menace, 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, attached.

References: 1. Honsberger NA, Six RH, Heinz TJ, Weber A, Mahabir SP, Berg TC. Efficacy of sarolaner in the prevention of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* transmission from infected *Ixodes scapularis* to dogs. *Vet Parasitol.* 2016;222:67-72. **2.** Six RH, Geurden T, et al. Evaluation of the speed of kill of sarolaner (Simparica™) against induced infestations of three species of ticks (*Amblyomma maculatum, Ixodes scapularis, Ixodes ricinus*) on dogs. Veterinary Parasitology 2016 May 30(222):37-42

ZOETIS PETCARE

Simparica®
(sarolaner) Chewables

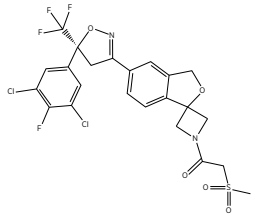
FOR ORAL USE IN DOGS ONLY

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.

The chemical structure of the S-enantiomer of sarolaner is:



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 and pets. 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**).

Precautions:
SIMPARICA may cause abnormal neurologic signs such as tremors, decreased conscious proprioception, ataxia, decreased or absent menace, and/or seizures (see **Animal Safety**).

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.

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

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.

NADA #141-452, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Made in Switzerland

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