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 aren’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 treat and control 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 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 the diagnostics 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® eLyme 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.
Kills deer ticks fast

Simparica Trio demonstrated ≥ 94.2% efficacy against existing infestations 24 hours after treatment

- Lyme is typically transmitted in 24 to 48 hours

In a study, Simparica blocked the transmission of Lyme from *Ixodes scapularis* (Black-legged “deer” tick)\(^1\)

- Simparica demonstrated 98.8% efficacy against existing infestations 12 hours after treatment\(^2\)
  - Maintained a rapid speed of kill throughout the month.

In a study, Simparica blocked the transmission of *Borrelia burgdorferi* from deer ticks to dogs\(^1\)

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 blocked the transmission of Lyme disease.

### Lyme Disease

**Presence of Borrelia burgdorferi**

<table>
<thead>
<tr>
<th>Antibody Test</th>
<th>ALL SIMPARICA DOGS TESTED</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP® 4Dx®</td>
<td>NEGATIVE!</td>
<td>6 OUT OF 8 DOGS WERE POSITIVE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCR and Culture</th>
<th>ALL SIMPARICA DOGS TESTED</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEGATIVE!</td>
<td>7 OUT OF 8 DOGS WERE POSITIVE</td>
</tr>
</tbody>
</table>

**References:**
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 whipworms or tapeworms demonstrated in the fecal sample, we will provide you Cestex (epsiprantel) free of charge or 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."
**Moxidectin** is a semi-synthetic methoxime derivative of nemadectin which (5 mg/kg) pyrantel (as pamoate salt).

**Cepphalo caninum** Toxascaris leonina and adult hookworm (Toxocara canis) or started at least one month before fleas become active. SIMPARICA TRIO should be administered year-round at monthly intervals for dogs and cats within a household with a flea control product. To minimize the likelihood of flea re-infestation, it is important to treat all animals of the former medication.

**Sarolaner** is an isoxazoline class of parasiticides and the chemical name is (E)-1,4,5,6-tetrahydro-1-methyl-2-(2-thienyl) vinyl) pyrimidine 4,4-methylbenzene [3-hydroxy-2-naphthaldehyde] (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 prevents heartworm disease caused by Dirofilaria immitis, kills adult fleas (Ctenocephalides felis) and is indicated for the treatment and prevention of flea infestations, the treatment and control of tick infestations with *Amblyomma americanum* (lone star tick), *Alypomma maculatum* (Salt Coast tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), and *Rhipicephalus sanguineus* (brown dog tick), and the treatment and control of *P. tenuipes* (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina* and adult hookworms (*Ancylostoma caninum* and *Unicauria stenocephala*) infections in one month and pups/girls 8 weeks of age and older, and weighing 5.8 pounds or greater. **DOSEAGE AND ADMINISTRATION** SIMPARICA TRIO is given orally once a month, at the recommended minimum dose of 0.34 mg/kg (1.2 mg/kg) sarolaner, 0.011 mg/lb (24 mg/kg) moxidectin, and 2.27 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

**Dosage Schedule**

<table>
<thead>
<tr>
<th>Body Weight (lbs)</th>
<th>Sarolaner per Tablet (mg)</th>
<th>Moxidectin per Tablet (mg)</th>
<th>Pyrantel per Tablet (mg)</th>
<th>Number of Tablets Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 to 5.5</td>
<td>3</td>
<td>0.06</td>
<td>12.5</td>
<td>One</td>
</tr>
<tr>
<td>5.6 to 11.0</td>
<td>6</td>
<td>0.12</td>
<td>25</td>
<td>One</td>
</tr>
<tr>
<td>11.1 to 22.0</td>
<td>12</td>
<td>0.24</td>
<td>50</td>
<td>One</td>
</tr>
<tr>
<td>22.1 to 44.0</td>
<td>24</td>
<td>0.48</td>
<td>100</td>
<td>One</td>
</tr>
<tr>
<td>44.1 to 88.0</td>
<td>48</td>
<td>0.96</td>
<td>200</td>
<td>One</td>
</tr>
<tr>
<td>88.1 to 122.0</td>
<td>72</td>
<td>1.44</td>
<td>300</td>
<td>One</td>
</tr>
<tr>
<td>&gt;122.0</td>
<td>Administer the appropriate combination of tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 moxidectin 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 treatment 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>
<thead>
<tr>
<th>Clinical Sign</th>
<th>SIMPARICA TRIO n = 272</th>
<th>Active Control n = 138</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>14.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.2%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>8.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5.1%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Porytlia</td>
<td>3.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypertecstis</td>
<td>2.2%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Polyptosis</td>
<td>2.2%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

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.

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/animaldrugs.
**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 parasiticide and the chemical name is 1-[(5’R)-5’-(3,5-Dichloro-4-fluorophenyl)-5-(3’(trifluoromethyl)-4’-dihydroisoxazol-3’-yl)-3’-H-pipecolin-azetidin-3’(2’)-benzofuran]-1-(pi)-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:

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>SAROLANER per Tablet (mg)</th>
<th>Number of Tablets Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 to 5.5 lbs</td>
<td>5</td>
<td>One</td>
</tr>
<tr>
<td>5.6 to 10.0 lbs</td>
<td>10</td>
<td>One</td>
</tr>
<tr>
<td>11.1 to 22.0 lbs</td>
<td>20</td>
<td>One</td>
</tr>
<tr>
<td>22.1 to 44.0 lbs</td>
<td>40</td>
<td>One</td>
</tr>
<tr>
<td>44.1 to 88.0 lbs</td>
<td>80</td>
<td>One</td>
</tr>
<tr>
<td>88.1 to 132.0 lbs</td>
<td>120</td>
<td>One</td>
</tr>
<tr>
<td>&gt;132.1 lbs</td>
<td>Administer the appropriate combination of tablets</td>
<td></td>
</tr>
</tbody>
</table>

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.

**Tick Treatment and Prevention:**
Treatments with SIMPARICA may begin at any time of the year. In areas where fleas are common year-round, monthly treatments 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.

**Flea Treatment and Prevention:**
Treatment with SIMPARICA may begin at any time of the year. In areas where fleas are common year-round, monthly treatments 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.

**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 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. SIMPARICA was administered in a well-controlled US field study, which included a total of 479 dogs. Abnormal neurologic signs such as tremors, decreased conscious proprioception, ataxia, decreased or absent menace, and/or seizures were reported in dogs 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.

**Adverse Reactions:**
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, 17, 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 and ataxia post-dose on Day 1. In the 5X group, one female dog had a seizure on Day 61 (5 days after third dose); one male 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 results 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 Cmax more than 7-fold higher than the mean Cmax 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

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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.