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-dihydroxy-5-oxo-4-phenyl-1H-isooxazol-3-yl)-3-benzofuran-2-yl)-(2-methylsulfonyl)ethaneone. SIMPARICA contains the 5-enantiomer of sarolaner.

Indications:
SIMPARICA kills adult fleas, and is indicated for the prevention and treatment 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 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).

<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 11.0 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. 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:
- 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 young children 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>
<thead>
<tr>
<th>Adverse reaction</th>
<th>sarolaner</th>
<th>sarolaner</th>
<th>active control</th>
<th>active control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% (n = 315)</td>
<td>N</td>
<td>% (n = 164)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>0.95%</td>
<td>9</td>
<td>5.50%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0.63%</td>
<td>2</td>
<td>1.20%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1</td>
<td>0.32%</td>
<td>2</td>
<td>1.20%</td>
</tr>
<tr>
<td>Inappetence</td>
<td>0</td>
<td>0%</td>
<td>3</td>
<td>1.80%</td>
</tr>
</tbody>
</table>

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 use from 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/reportanadverse.

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) 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_max 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. Sarolaner is a high affinity (99.6%) 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 at 4X, 9X, and 10X respectively.

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 GABA (GABA-A) receptor and glutamate receptor, and works at the neuromuscular junction in insects. This results in uncontrolled neuromuscular activity leading to death in insects or arachnids.

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 ≥48 hours 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, 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 ≥39%, ≥99%, 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 1, one female dog exhibited tremors on Days 1, 2, and 3, and one female dog exhibited tremors post-dose 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 groups. 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 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.

Distributed by: Zoetis Inc. Kalamazoo, MI 49007

Revised: June 2019
S0070902A&P