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.

SIMPARICA is a member of the isoxazoline class of saranilides and the chemical name is 1-(5-(1S)-5-(3S)-5-chloro-4-fluorophenyl)-5-( trifluoromethyl)-1-L-threo(propanoic acid)-3-(3-H- isoproazetidin-1'-yl)-2-(methylsulfonyl)ethanone. SIMPARICA contains the S-enantiomer of sarolaner.

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

Additional Note: One female dog aged 8.6 years exhibited lethargy, ataxia while posturing to eliminate, elevated third eyelid, 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.Zoetis.com. For additional information about adverse drug reactions, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Clinical Pharmacology:
SIMPARICA is rapidly and well absorbed following oral administration of SIMPARICA. In a study of 12 Beagle dogs the mean maximum plasma concentration (Cmax) was 1100 ng/ml, and the mean time to maximum plasma concentration (Tmax) 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 t½ values for fasted and fed animals was 10 and 12 days respectively. SIMPARICA is distributed widely; the mean volume of distribution (Vss) was 2.81 kg/body weight following a 2 mg/kg intravenous dose of sarolaner. SIMPARICA is highly bound (89.9%) 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 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 isoxazolone 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 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 >86.2% 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 reinfection for 30 days.

In a well-controlled 90-day field study conducted in households with existing fleas, SIMPARICA demonstrated >99% effectiveness against all stages of fleas. SIMPARICA prevented new infestations of all stages of fleas.

Animal Safety:
In a margin of safety study, SIMPARICA was administered orally to 8-week-old Beagle puppies at doses of 0, 1X, and 3X the maximum recommended dose (4 mg/kg) for 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, 5, and 7; and one female dog exhibited tremors on Day 1, and male 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 3X group two hours after dosing on Day 140 (dose 6). There were no treatment-related neurologic 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 neurologic signs including ataxia, tremors, disorientation, hyperactivity, diminished proprioception, and ataxia since post-dose on Day 0. 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 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) Chews 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.

Zoetis Inc.
Kalamazoo, MI 49007
Made in Switzerland
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Table 1: Dogs with adverse reactions

<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>N</td>
<td>% (n = 315)</td>
<td>N</td>
<td>% (n = 164)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>0.95%</td>
<td>9</td>
<td>5.30%</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>
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