

Date of Approval: May 18, 2021

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-452

Simparica®

sarolaner

Chewable Tablet

Dogs

This supplement provides for the addition of the indication, "for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks."

Sponsored by:

Zoetis Inc.

Executive Summary

Simparica® (sarolaner) chewable tablets are approved for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks. *B. burgdorferi* are spirochete bacteria that can cause Lyme disease in infected dogs. The bacteria are transmitted to a dog through the bite of infected *I. scapularis* ticks, also called black-legged ticks. Simparica® was previously shown to be effective against *I. scapularis* ticks for one month in dogs. The studies that support this supplemental approval showed that the drug kills *I. scapularis* ticks on the treated dogs before they can transmit *B. burgdorferi* to the dogs.

Simparica® is already approved to kill adult fleas, to treat and prevent flea infestations (*Ctenocephalides felis*), and to treat and control several types of tick infestations for one month in dogs 6 months of age or older, and weighing 2.8 pounds or greater. Simparica® is given orally once a month.

Sarolaner is an ectoparasiticide belonging to the isoxazoline group. The drug inhibits gamma-aminobutyric acid (GABA)-gated chloride channels in fleas and ticks. Chloride ions are blocked from crossing cell membranes, which results in uncontrolled neuromuscular activity in fleas and ticks, causing their death. Sarolaner is selectively toxic to fleas and ticks because their GABA receptors are more sensitive to the drug than mammalian GABA receptors.

Proprietary Name	Established Name	Application Type and Number	Sponsor
Simparica®	sarolaner	New Animal Drug Application (NADA) 141-452	Zoetis Inc.

Safety and Effectiveness

The sponsor conducted two laboratory studies to show that Simparica® protects dogs from infection with *B. burgdorferi* by killing the infected *I. scapularis* ticks on the dogs before they can transmit the bacteria. In each study, dogs were treated with either Simparica® or placebo on Day 0 and then experimentally infested with viable, unfed, adult *I. scapularis* ticks on Day 28. At least sixty percent of the ticks were infected with *B. burgdorferi*. The ticks were counted and removed on Day 33.

Blood samples were collected from all dogs on multiple days throughout the study, from 10 days before treatment to 104 days after treatment. The samples were both qualitatively and quantitatively tested for *B. burgdorferi* antibodies. Skin biopsies from each dog were collected on Day 104 from the heaviest areas of tick attachment, as marked on Day 33, and were quantitatively tested for *B. burgdorferi* by polymerase chain reaction (PCR) testing.

In both studies, Simparica® was greater than 96% effective at killing *I. scapularis* ticks for 33 days in treated dogs, while dogs in the control group remained infested with live ticks. Simparica® was also 100% effective at preventing *B. burgdorferi* infections as a direct result of killing *I. scapularis* ticks. All treated dogs remained seronegative for *B. burgdorferi* throughout the study and the bacteria were not detected by PCR testing of the skin biopsies. In contrast, most of the dogs in the

control group became seropositive for *B. burgdorferi* and the bacteria were detected by PCR testing of the skin biopsies. No adverse reactions were seen in either study. The Freedom of Information (FOI) Summary for the original approval of Simparica[®], dated February 24, 2016, contains a summary of target animal safety studies in dogs.

Conclusions

Based on the data submitted by the sponsor for the approval of Simparica[®], FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

NADA 141-452

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Simparica®

D. Drug Product Established Name

Sarolaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable Tablet

G. Amount of Active Ingredient

Six tablet sizes 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, and 120 mg.

H. How Supplied

Each tablet size is available in color-coded packages of one, three, or six tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

2 mg/kg body weight, once per month

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

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.

N. Effect of Supplement

This supplement provides for the addition of the indication, "for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks."

II. EFFECTIVENESS

The effectiveness of Simparica® was demonstrated in the two well-controlled laboratory studies described below. No treatment-related adverse reactions were reported in any of the twenty dogs administered the labeled dose. These studies demonstrated that Simparica® is effective in preventing *Borrelia burgdorferi* infections by killing *Ixodes scapularis* ticks on the dogs before they could transmit the infection. The supplemental approval of NADA 141-452, dated December 12, 2016, demonstrated that Simparica® is effective against *I. scapularis* ticks for 35 days.

A. Dosage Characterization

This supplemental approval does not change the previously approved 2 mg/kg (0.91 mg/lb) dose, given orally once a month. The Freedom of Information (FOI) Summary for the original approval of NADA 141-452 dated February 24, 2016, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study

Title: Evaluation of the Ability of Simparica® to Prevent the Transmission of *Borrelia burgdorferi* from Infected *Ixodes scapularis* to Dogs. (Study No. A162C-US-19-A71)

Study Dates: December 5, 2019 to November 12, 2020

Study Location: Kalamazoo, MI

Study Design:

Objective: To evaluate the ability of Simparica® to protect dogs against *Borrelia burgdorferi* infections from wild caught *Ixodes scapularis* ticks by killing the ticks before transmission may occur.

Study Animals: Twenty (20) Beagle dogs (11 male and 9 female), 11 months of age, and 7.7 to 12.2 kg body weight

Experimental Design: This study was a placebo-controlled, masked, completely randomized study design conducted in accordance with Good Clinical Practices. The study included two treatment groups of 10 dogs per group. One group was administered a placebo and one group was administered Simparica® at a dose of 2.0 mg/kg. The treatment was administered on Day 0. Each dog was infested with approximately 50 unfed, wild-caught, adult *I. scapularis* ticks (approximately equal numbers of males and females) on Day 28. The ticks had a *B. burgdorferi* infection rate of 60%. The ticks were counted and removed on Day 33.

Table II.1. Treatment groups for Study A162C-US-19-A71

Group	Treatment	Dosage ¹	Day of Treatment	Dogs per Group	Day of Infestation	Day of Tick Count with Removal	Days of Blood Collection	Day of Skin Biopsy Collection
T01	Placebo	NA	Day 0	10	28	33	-10, 27, 49, 63, 77, 91 and 104	104
T02	Simparica® (sarolaner)	2.0 mg/kg	Day 0	10	28	33	-10, 27, 49, 63, 77, 91 and 104	104

¹ Minimum Dosage

Drug Administration: All treatments were administered orally.

Measurements and Observations: General health observations were conducted at least once daily. Blood samples were collected from each dog on Days -10, 27, 49, 63, 77, 91, and 104, and qualitatively tested for *B. burgdorferi* antibodies using the SNAP® 4Dx® Plus Test. Blood samples were also quantitatively assayed for *B. burgdorferi* antibodies using Lyme Quant C6® antibody tests. Four skin biopsies from each dog were collected on Day 104 from the heaviest areas of tick attachment, as marked on Day 33, and were tested by PCR for the quantitative presence of *B. burgdorferi*. Due to a sample processing error that occurred with the Day 49 Lyme Quant C6® antibody tests, these results were excluded from the data analysis and summaries.

Statistical Methods:

Tick Counts: Percent effectiveness of the Simparica®-treated group with respect to the placebo-treated group was calculated for Day 33 using the formula $[(C - T) / C] \times 100$, where C = arithmetic mean of live tick counts for the placebo-treated group and T = arithmetic mean of live tick counts for the Simparica®- treated group. Arithmetic means for live tick counts were estimated using the least squares means obtained from the statistical model.

Serology: A dog was considered to be infected with *B. burgdorferi* if a positive result was obtained on any of the SNAP® 4Dx® Plus tests for *B. burgdorferi* after Day 28, or the Lyme Quant C6® tests (titer ≥ 30 U/mL) after Day 28, or on PCR tests from any of the four skin biopsies collected on Day 104. For a

dog to be considered not infected with *B. burgdorferi*, a negative result must be obtained for both serology tests at all sampling time points after Day 28 and for the PCR tests from all four skin biopsies collected on Day 104.

The proportion of animals infected (Yes/No) with *B. burgdorferi* in the Simparica[®]-treated group was compared to the proportion of infected animals infected in the placebo group using Fisher's Exact Test. The statistical test was performed at a significance level of 0.05 (two-sided).

Results: Placebo group dogs maintained adequate tick infestations on day 33 with at least six of the ten dogs having 12 or more live ticks. The percent reduction in arithmetic mean live tick counts in the Simparica[®]-treated group compared to the placebo group on Day 33 was 96.5%. Mean live tick counts for the Simparica[®]-treated group was significantly lower than the placebo group ($P < 0.0001$).

Table II.2. *I. scapularis* Live Tick Effectiveness: Arithmetic Mean Live Tick Count (Percent Effectiveness)

Day of Tick Count	Placebo Group Arithmetic Mean Live Tick Count	Simparica [®] Group Arithmetic Mean Live Tick Count	Percent Effectiveness
33	19.8	0.7	96.5%

All dogs were seronegative for *B. burgdorferi* before treatment and tick infestations with negative test results on both the SNAP[®] 4Dx[®] Plus tests and Lyme Quant C6[®] tests (titer < 30 U/mL).

Nine of the ten placebo group dogs were determined to be infected with *B. burgdorferi* with positive test results obtained on the SNAP[®] 4Dx[®] Plus test for *B. burgdorferi* and the Lyme Quant C6[®] test (titer ≥ 30 U/mL) on and after Day 63, and the detection of *B. burgdorferi* on PCR from at least one of the four skin biopsies collected on Day 104. One placebo group dog remained seronegative throughout the study and *B. burgdorferi* was not detected via PCR testing for any of the four skin biopsies collected on Day 104.

All Simparica[®]-treated dogs were determined to not have been infected with *B. burgdorferi* by remaining seronegative throughout the study with none of the SNAP[®] 4Dx[®] Plus tests for *B. burgdorferi* or the Lyme Quant C6[®] tests (titer ≥ 30 U/mL) positive at any timepoint, in addition to no detection of *B. burgdorferi* via PCR for all skin biopsies collected on Day 104, indicating prevention of *B. burgdorferi* infection. The proportion of dogs positive for *B. burgdorferi* in the Simparica[®]-treated group was significantly different than the placebo-treated group ($P = 0.0001$).

Table II.3. SNAP® 4Dx® Plus results

Study Day	Placebo Dogs Positive for <i>B. burgdorferi</i>	Simparica®-Treated Dogs Positive for <i>B. burgdorferi</i>
-10	0/10	0/10
27	0/10	0/10
49	0/10	0/10
63	9/10	0/10
77	9/10	0/10
91	9/10	0/10
104	9/10	0/10

Table II.4. Lyme Quant C6® results

Study Day	Placebo Dogs Positive for <i>B. burgdorferi</i>	Simparica®-Treated Dogs Positive for <i>B. burgdorferi</i>
-10	0/10	0/10
27	0/10	0/10
63	9/10	0/10
77	9/10	0/10
91	9/10	0/10
104	9/10	0/10

Table II.5. PCR results

Study Day	Placebo Dogs Positive for <i>B. burgdorferi</i>	Simparica®-Treated Dogs Positive for <i>B. burgdorferi</i>
104	9/10	0/10

Adverse Reactions: There were no treatment-related adverse reactions during the study.

Conclusion: A single oral dose of Simparica® administered orally to dogs 28 days prior to infestation with *B. burgdorferi*-infected *Ixodes scapularis* ticks prevented *B. burgdorferi* infections as a direct result of killing the *Ixodes scapularis* vector ticks.

2. Laboratory Dose Confirmation Study

Title: Evaluation of the Ability of Simparica® to Prevent the Transmission of *Borrelia burgdorferi* from Infected *Ixodes scapularis* to Dogs. (Study No. A162C-US-19-A74)

Study Dates: December 5, 2019 to November 11, 2020

Study Location: Athens, GA

Study Design:

Objective: To evaluate the ability of Simparica® to protect dogs against *Borrelia burgdorferi* infections from wild caught *Ixodes scapularis* ticks by killing the ticks before transmission may occur.

Study Animals: Twenty (20) Beagle dogs (8 male and 12 female), 9 months of age, and 5.1 to 8.7 kg body weight.

Experimental Design: This study was a placebo-controlled, masked, completely randomized study design conducted in accordance with Good Clinical Practices. The study included two treatment groups of 10 dogs per group. One group was administered a placebo and one group was administered Simparica® at a dose of 2.0 mg/kg. The treatment was administered on Day 0. Each dog was infested with approximately 50 unfed, wild-caught, adult *I. scapularis* ticks (approximately equal numbers of males and females) on Day 28. The ticks had a *B. burgdorferi* infection rate of 75%. The ticks were counted and removed on Day 33.

Table II.6. Treatment groups for Study A162C-US-19-A74

Group	Treatment	Dosage ¹	Day of Treatment	Dogs per Group	Day of Infestation	Day of Tick Count with Removal	Days of Blood Collection	Day of Skin Biopsy Collection
T01	Placebo	NA	Day 0	10	28	33	-9, 27, 49, 63, 77, 91 and 104	104
T02	Simparica® (sarolaner)	2.0 mg/kg	Day 0	10	28	33	-9, 27, 49, 63, 77, 91 and 104	104

¹ Minimum Dosage

Drug Administration: All treatments were administered orally.

Measurements and Observations: General health observations were conducted at least once daily. Blood samples were collected from each dog on Days -9, 27, 49, 63, 77, 91, and 104, and qualitatively tested for *B. burgdorferi* antibodies using the SNAP® 4Dx® Plus Test. Blood samples were also quantitatively assayed for *B. burgdorferi* antibodies using Lyme Quant C6® antibody tests. Four skin biopsies from each dog were collected on Day 104 from the heaviest areas of tick attachment, as marked on Day 33, and were tested by PCR for the quantitative presence of *B. burgdorferi*. Due to a sample processing error that occurred with the Day 49 Lyme Quant C6® antibody tests, these results were excluded from the data analysis and summaries.

Statistical Methods:

Tick Counts: Percent effectiveness of the Simparica®-treated group with respect to the placebo-treated group was calculated for Day 33 using the formula $[(C - T) / C] \times 100$, where C = arithmetic mean of live tick counts for the placebo-treated group and T = arithmetic mean of live tick counts for the

Simparica[®]- treated group. Arithmetic means for live tick counts were estimated using the least squares means obtained from the statistical model.

Serology: A dog was considered to be infected with *B. burgdorferi* if a positive result was obtained on any of the SNAP[®] 4Dx[®] Plus tests for *B. burgdorferi* after Day 28, or the Lyme Quant C6[®] tests (titer \geq 30 U/mL) after Day 28, or on PCR tests from any of the four skin biopsies collected on Day 104. For a dog to be considered not infected with *B. burgdorferi*, a negative result must be obtained for both serology tests at all sampling time points after Day 28 and for the PCR tests from all four skin biopsies collected on Day 104.

The proportion of animals infected (Yes/No) with *B. burgdorferi* in the Simparica[®] group was compared to the proportion of infected animals in the placebo-treated group using Fisher's Exact Test. The statistical test was performed at a significance level of 0.05 (two-sided).

Results: Placebo group dogs maintained adequate tick infestations on day 33 with at least six of the ten dogs having 12 or more live ticks. The percent reduction in arithmetic mean live tick counts in the Simparica[®]-treated group compared to placebo on Day 33 was 100%. Mean live tick counts for the Simparica[®]-treated group was significantly lower than the placebo group ($P < 0.0001$).

Table II.7. I. scapularis Live Tick Effectiveness; Arithmetic Mean Live Tick Count (Percent Effectiveness)

Day of Tick Count	Placebo Group Arithmetic Mean Live Tick Count	Simparica [®] Group Arithmetic Mean Live Tick Count	Percent Effectiveness
33	23.6	0	100%

All dogs were seronegative for *B. burgdorferi* before treatment and tick infestations with negative test results on both the SNAP[®] 4Dx[®] Plus tests and Lyme Quant C6[®] tests (titer $<$ 30 U/mL).

All ten placebo group dogs were determined to be infected with *B. burgdorferi* with positive test results obtained on the SNAP[®] 4Dx[®] Plus test for *B. burgdorferi* and the Lyme Quant C6[®] test (titer \geq 30 U/mL) on and after Day 77, and the detection of *B. burgdorferi* on PCR from at least one of the four skin biopsies collected on Day 104.

All Simparica[®]-treated dogs were determined to not have been infected with *B. burgdorferi* by remaining seronegative throughout the study with none of the SNAP[®] 4Dx[®] Plus tests for *B. burgdorferi* or the Lyme Quant C6[®] tests (titer \geq 30 U/mL) positive at any timepoint, in addition to no detection of *B. burgdorferi* via PCR for all skin biopsies collected on Day 104, indicating prevention of *B. burgdorferi* infection. The proportion of dogs positive for *B. burgdorferi* in the Simparica[®]-treated group was significantly different than the placebo group ($P < 0.0001$).

Table II.8. SNAP® 4Dx® Plus results

Study Day	Placebo Dogs Positive for <i>B. burgdorferi</i>	Simparica®-Treated Dogs Positive for <i>B. burgdorferi</i>
-9	0/10	0/10
27	0/10	0/10
49	1/10	0/10
63	9/10	0/10
77	10/10	0/10
91	10/10	0/10
104	10/10	0/10

Table II.9. Lyme Quant C6® results

Study Day	Placebo Dogs Positive for <i>B. burgdorferi</i>	Simparica®-Treated Dogs Positive for <i>B. burgdorferi</i>
-9	0/10	0/10
27	0/10	0/10
63	8/10	0/10
77	10/10	0/10
91	10/10	0/10
104	10/10	0/10

Table II.10. PCR results

Study Day	Placebo Dogs Positive for <i>B. burgdorferi</i>	Simparica®-Treated Dogs Positive for <i>B. burgdorferi</i>
104	10/10	0/10

Adverse Reactions: There were no treatment-related adverse reactions during the study.

Conclusion: A single oral dose of Simparica® administered to dogs 28 days prior to infestation with *B. burgdorferi*-infected *Ixodes scapularis* ticks prevented *B. burgdorferi* infections as a direct result of killing the *Ixodes scapularis* vector ticks.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-452 dated February 24, 2016, contains a summary of target animal safety studies for dogs.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Simparica®:

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

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Simparica®, when used according to the label, is safe and effective for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

A. Marketing Status

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to monitor for and respond to adverse reactions.

B. Exclusivity

This supplemental approval for Simparica® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indication, "for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks."

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.