Date of Approval: April 8, 2025

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-521

Simparica TRIO®

(sarolaner, moxidectin, and pyrantel chewable tablets)

Dogs

This supplement provides for the addition of the indication for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated dog for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater.

Sponsored by:

Zoetis Inc.

Executive Summary

Simparica TRIO® (sarolaner, moxidectin, and pyrantel chewable tablets) is approved for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated dog for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater.

Simparica TRIO® is already approved to prevent heartworm disease caused by *Dirofilaria immitis,* and to treat and control roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and hookworm (L4, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*) infections. In addition, Simparica TRIO® is also already approved to kill adult fleas *(Ctenocephalides felis)* and to treat and prevent flea infestations and to treat and control tick infestations with *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (Asian longhorned tick) for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater. Lastly, Simparica TRIO® is also already approved to prevent *Borrelia burgdorferi* infections as a direct result of killing *I. scapularis* vector ticks.

Simparica TRIO® is an antiparasitic drug with three active ingredients and is available in six strengths of flavored chewable tablets that are given orally once a month.

Safety and Effectiveness

The sponsor conducted two laboratory studies in healthy, male and female, beagle and mixed-breed dogs. In each study, the dogs were experimentally infested on Days 0, 7, 14, 21, and 30 with adult *C. felis* fleas that were infected with *D. caninum*. On Day 0, dogs were administered either Simparica TRIO® or a placebo control tablet by mouth. Flea counts were performed on Day 33 (72 hours after the last flea infestation), and on Day 58 the dogs were humanely euthanized and necropsied for recovery of *D. caninum*. Scolex counts were performed on Day 58. The scolex is the attachment organ of the tapeworm that anchors the parasite to the host's intestinal wall.

In both studies, Simparica TRIO® was 100% effective at killing adult fleas. On Day 33, all dogs in the treatment groups had no fleas, while dogs in the control groups remained infested. In both studies, Simparica TRIO® was over 92% effective at preventing *D. caninum* infections. On Day 58, dogs in the treatment groups had lower mean scolex counts compared to dogs in the control groups. One dog in one of the studies had self-limiting diarrhea after treatment with Simparica TRIO®. No other adverse reactions were observed.

The Freedom of Information (FOI) Summary for the original approval of Simparica TRIO®, dated February 27, 2020, contains a summary of target animal safety studies for dogs.

Conclusions

Based on the data submitted by the sponsor for the approval of Simparica TRIO®, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-521

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Simparica TRIO®

D. Drug Product Established Name

sarolaner, moxidectin, and pyrantel chewable tablets

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable Tablet

G. Amount of Active Ingredient

Each chewable tablet contains:

3 mg sarolaner/ 0.06 mg moxidectin/ 12.5 mg pyrantel (as pamoate salt)
6 mg sarolaner/ 0.12 mg moxidectin/ 25 mg pyrantel (as pamoate salt)
12 mg sarolaner/ 0.24 mg moxidectin/ 50 mg pyrantel (as pamoate salt)
24 mg sarolaner/ 0.48 mg moxidectin/ 100 mg pyrantel (as pamoate salt)
48 mg sarolaner/ 0.96 mg moxidectin/ 200 mg pyrantel (as pamoate salt)
72 mg sarolaner/ 1.44 mg moxidectin/ 300 mg pyrantel (as pamoate salt)

H. How Supplied

Simparica TRIO® (sarolaner, moxidectin, and pyrantel chewable tablets) is available in six flavored tablet sizes. Each tablet size is available in packages of one, three, or six tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Simparica TRIO® is given orally once a month, at the recommended minimum dose of 0.54 mg/lb (1.2 mg/kg) sarolaner, 0.011 mg/lb (24 µg/kg) moxidectin, and 2.27 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

Dosage Schedule

Body Weight (lbs)	Sarolaner per Tablet (mg)	Moxidectin per Tablet (mg)	Pyrantel per Tablet (mg)	Number of Tablets Administered
2.8 to 5.5	3	0.06	12.5	One
5.6 to 11	6	0.12	25	One
11.1 to 22	12	0.24	50	One
22.1 to 44	24	0.48	100	One
44.1 to 88	48	0.96	200	One
88.1 to 132	72	1.44	300	One
>132	Administer the appropriate combination of tablets			

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

Simparica TRIO® is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and hookworm (L4, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*) infections. Simparica TRIO® kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment and prevention of flea infestations, the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated dog, and the treatment and control of tick infestations with *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (Asian longhorned tick) for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater. Simparica TRIO® 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 *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated dog for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater.

II. EFFECTIVENESS

The effectiveness of Simparica TRIO® for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated dog was demonstrated in two well-controlled laboratory studies (A166C-ZA-22-C42 and A166C-US-22-C41) described below.

A. Dosage Characterization

This supplemental approval does not change the previously approved doses of sarolaner (0.54 mg/lb; 1.2 mg/kg), moxidectin (0.011 mg/lb; 24 µg/kg), and (pyrantel 2.27 mg/lb; 5 mg/kg) (as pamoate salt), given orally once a month. The FOI Summary for the original approval of NADA 141-521 dated February 27, 2020, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study A166C-ZA-22-C42

   Title: Prevention of *Dipylidium caninum* Infections in Dogs as a Direct Result of Killing *Ctenocephalides felis* on Dogs. (Study No. A166C-ZA-22-C42)

   Study Dates: August 23, 2022 to September 29, 2023

   Study Location: Bloemfontein, South Africa

   Study Design:

   Objective: To evaluate the effectiveness of a single oral administration of Simparica TRIO® for the prevention of *Dipylidium caninum* infection by killing the flea intermediate host for one month in dogs with induced infestations of *Ctenocephalides felis*.

   Study Animals: Twenty beagle and mixed-breed dogs (4 males and 16 females), 21 to 95 months of age, and 12.7 to 28.6 kg body weight.

   Experimental Design: This study was a placebo-controlled, masked, randomized complete block study design. Dogs were randomly assigned to the control group (10 dogs) or the Simparica TRIO® group (10 dogs). Each dog was infested with approximately 200 *D. caninum*-infected *C. felis* fleas on Days 0, 7, 14, 21, and 30. Fleas were counted and removed on Day 33. The study was conducted in accordance with Good Clinical Practice (GCP) guidance.

Table II.1. Treatment Groups (Study No. A166C-ZA-22-C42)

Treatment Group	Treatment	Day of Treatment	Dogs per Group	Days of Flea Infestation	Day of Flea Count	Day of Scolex Count
T01	Control*	Day 0	10	Days 0, 7, 14, 21, 30	Day 33	Day 58
T02	Simparica TRIO®	Day 0	10	Days 0, 7, 14, 21, 30	Day 33	Day 58

*Pet-Tabs® chewable tablet (flavored vitamin and mineral supplement)

Drug Administration: Dogs were fasted 12 hours prior to administration and were administered Simparica TRIO® or control tablet by mouth on Day 0. One dog in the control group was incorrectly dosed and excluded from the effectiveness analysis.

Measurements and Observations: General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment on Day 0 and at 1, 3, 6, and 24 hours after treatment. Fleas were counted and removed on Day 33. On Day 58, the dogs were humanely euthanized and necropsied for recovery of *D. caninum* and counting of scoleces.

Statistical Methods:

Flea Counts: The flea counts were analyzed with a generalized linear mixed model with a fixed effect of treatment, and random effects of room and block within room. Least squares mean (LSM) counts were reported by treatment group. Comparison of mean flea counts was conducted between the Simparica TRIO® group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the Simparica TRIO® group with respect to the control group was calculated using the formula [(C–T)/C] X 100, where C = LSM of flea counts for the control group and T = LSM of flea counts for the Simparica TRIO® group.

Scolex Counts: The scolex counts were transformed with a natural logarithm transformation prior to analysis with a generalized linear mixed model. The model contained a fixed effect of treatment, and the random effects of room and block within room. Geometric mean was obtained through back-transformation of the LSM estimated from the model. Comparison of mean scolex counts was conducted between the Simparica TRIO® group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the Simparica TRIO® group with respect to the control group was calculated using the formula [(C–T)/C] X 100, where C = geometric mean of scolex counts for the control group and T = geometric mean of scolex counts for the Simparica TRIO® group.

Results:

Flea Counts: The control group met the definition for adequate flea infestation with at least 6 of the 9 dogs having ≥50 fleas following the final flea infestation on Day 30.

The mean flea count for the Simparica TRIO® group was significantly different compared to the control group on Day 33 ($p<0.0001$), demonstrating 100% effectiveness against fleas.

Table II.2. Day 33 LSM Flea Counts and Percent Effectiveness Against Fleas for Study A166C-ZA-22-C42

Control Group* LSM Flea Count	Simparica TRIO® LSM Flea Count	Percent Effectiveness
94.7	0	100%

*Only nine dogs are included in the control group due to incorrect dosing of one dog.

Scolex Counts: The control group met the definition for adequate infection with at least 6 of the 9 dogs having ≥2 scoleces at necropsy.

There was a significant difference in mean scolex counts ($p=0.0029$) for Simparica TRIO®-treated dogs compared to the control group, demonstrating 92.1% effectiveness for the prevention of *D. caninum* infection.

Table II.3. Day 58 Scolex Counts and Percent Effectiveness for the Prevention of *Dipylidium caninum* Infections for Study A166C-ZA-22-C42

Control Group* Geometric Mean Scolex Count	Simparica TRIO® Geometric Mean Scolex Count	Percent Effectiveness
5.2	0.4	92.1%

*Only nine dogs are included in the control group due to incorrect dosing of one dog.

Adverse Reactions: One dog in the Simparica TRIO® group had diarrhea one hour after treatment.

Conclusions: This study demonstrated the effectiveness of Simparica TRIO® for preventing the infection of *D. caninum* as a direct result of killing the vector flea, *C. felis*, on the treated dogs for one month.

2. Laboratory Dose Confirmation Study A166C-US-22-C41

Title: Prevention of *Dipylidium caninum* Infections in Dogs as a Direct Result of Killing *Ctenocephalides felis* on Dogs. (Study No. A166C-US-22-C41)

Study Dates: November 2, 2023 to September 21, 2024

Study Location: Waverly, NY

Study Design:

Objective: To evaluate the effectiveness of a single oral administration of Simparica TRIO® for the prevention of *Dipylidium caninum* infection by killing the flea intermediate host for one month in dogs with induced infestations of *Ctenocephalides felis*.

Study Animals: Twenty beagle and mixed-breed dogs (10 males and 10 females), 20 to 50 months of age, and 7.3 to 14.5 kg body weight.

Experimental Design: This study was a placebo-controlled, masked, randomized complete block study design. Dogs were randomly assigned to the control group (10 dogs) or the Simparica TRIO® group (10 dogs). Each dog was infested with approximately 200 *D. caninum*-infected *C. felis* fleas on Days 0, 7, 14, 21, and 30. Fleas were counted and removed on Day 33. The study was conducted in accordance with GCP guidance.

Table II.4. Treatment Groups (Study No. A166C-US-22-C41)

Treatment Group	Treatment	Day of Treatment	Dogs per Group	Days of Flea Infestation	Day of Flea Count	Day of Scolex Count
T01	Control*	Day 0	10	Days 0, 7, 14, 21, 30	Day 33	Day 58
T02	Simparica TRIO®	Day 0	10	Days 0, 7, 14, 21, 30	Day 33	Day 58

*Pet-Tabs® chewable tablet (flavored vitamin and mineral supplement)

Drug Administration: Dogs were fasted 12 hours prior to administration and were administered Simparica TRIO® or control tablet by mouth on Day 0.

Measurements and Observations: General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment on Day 0 and at 1, 3, 6, and 24 hours after treatment. Fleas were counted and removed on Day 33. On Day 58, the dogs were humanely euthanized and necropsied for recovery of *D. caninum* and counting of scoleces.

Statistical Methods:

Flea Counts: The flea counts were analyzed with a generalized linear mixed model with a fixed effect of treatment, and random effect of block. LSM counts were reported by treatment group. Comparison of mean flea counts was conducted between the Simparica TRIO® group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the Simparica TRIO® group with respect to the control group was calculated using the formula [(C–T)/C] X 100, where C = LSM of flea counts for the control group and T = LSM of flea counts for the Simparica TRIO® group.

Scolex Counts: The scolex counts were transformed with a natural logarithm transformation prior to analysis with a generalized linear mixed model. The model contained the fixed effect of treatment, and the random effect of block. Geometric

mean was obtained through back-transformation of the LSM estimated from the model. Comparison of mean scolex counts was conducted between the Simparica TRIO® group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the Simparica TRIO® group with respect to the control group was calculated using the formula [(C–T)/C] X 100, where C = geometric mean of scolex counts for the control group and T = geometric mean of scolex counts for the Simparica TRIO® group.

Results:

Flea Counts: The control group met the definition for adequate flea infestation with at least 6 of the 10 dogs having ≥50 fleas following the final flea infestation on Day 30.

The mean flea count for the Simparica TRIO® group was significantly different compared to the control group on Day 33 (p=0.0007), demonstrating 100% effectiveness against fleas.

Table II.5. Day 33 LSM Flea Counts and Percent Effectiveness Against Fleas for Study A166C-US-22-C41

Control Group LSM Flea Count	Simparica TRIO® LSM Flea Count	Percent Effectiveness
67.0	0	100%

Scolex Counts: The control group met the definition for adequate infection with at least 6 of the 10 dogs having ≥2 scoleces at necropsy.

There was a significant difference in mean scolex counts (p<0.0001) for Simparica TRIO®-treated dogs compared to the control group, demonstrating 100% effectiveness for the prevention of *D. caninum* infection.

Table II.6. Day 58 Scolex Counts and Percent Effectiveness for the Prevention of *Dipylidium caninum* Infections for Study A166C-US-22-C41

Control Group Geometric Mean Scolex Count	Simparica TRIO® Geometric Mean Scolex Count	Percent Effectiveness
15.9	0	100%

Adverse Reactions: No adverse reactions were observed during the study.

Conclusions: This study demonstrated the effectiveness of Simparica TRIO® for preventing the infection of *D. caninum* as a direct result of killing the vector flea, *C. felis*, on the treated dogs for one month.

III. TARGET ANIMAL SAFETY

FDA did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-521 dated February 27, 2020, 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, FDA 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 TRIO®:

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 TRIO®, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because the product is indicated for the prevention of heartworm infections (*D. immitis*) in dogs, which requires veterinary examination and testing to ensure dogs are negative for adult heartworm disease prior to administration of the product to dogs, and because professional expertise is required to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

This supplemental approval for Simparica TRIO® 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 *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated dog for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater.”

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval did not require a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

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