Date of Approval: November 6, 2024

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-521

SimparicaTRIO®

(sarolaner, moxidectin, and pyrantel chewable tablets)

Dogs

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations 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

SimparicaTRIO® (sarolaner, moxidectin, and pyrantel chewable tablets) is approved for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater. The Asian longhorned tick is a new tick species in the United States (U.S.). Not previously found in the Western Hemisphere, these ticks were reported for the first time in the U.S. in 2017.

SimparicaTRIO® 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 (immature adult and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*) infections. SimparicaTRIO® is also already approved to kill adult fleas (*Ctenocephalides felis*) and to treat and prevent flea infestations and for the treatment and control several types of tick infestations for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater. SimparicaTRIO® is also indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing the vector ticks.

SimparicaTRIO® 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 to show that SimparicaTRIO® is effective against *H. longicornis* tick infestations in dogs. In both studies, dogs were experimentally infested with viable, unfed, adult ticks on Day -2 and were re-infested on seven additional days during the study. On Day 0, dogs in the treated group were given SimparicaTRIO® and dogs in the control group were given a placebo tablet. Tick counts were performed on Day 2 (48 hours after treatment) and 48 hours after each re-infestation.

In both studies, SimparicaTRIO® was ≥99.6% effective at controlling *H. longicornis* tick infestations (reducing the number of live ticks) 48 hours after initial infestation and 48 hours after each re-infestation for one month, while dogs in the control group remained infested with live ticks at each tick count. SimparicaTRIO® was also effective in treating *H. longicornis* tick infestations (increasing the number of dead ticks). Compared to dogs in the control group, treated dogs had a higher number of dead ticks after all infestations. In one of the studies, one dog in the treated group had a seizure on Day 16.

The Freedom of Information (FOI) Summary for the original approval of SimparicaTRIO®, 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 SimparicaTRIO®, 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

SimparicaTRIO®

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:

3.0 mg sarolaner / 0.06 mg moxidectin / 12.5 mg pyrantel (as pamoate salt)
6.0 mg sarolaner / 0.12 mg moxidectin / 25 mg pyrantel (as pamoate salt)
12.0 mg sarolaner / 0.24 mg moxidectin / 50 mg pyrantel (as pamoate salt)
24.0 mg sarolaner / 0.48 mg moxidectin / 100 mg pyrantel (as pamoate salt)
48.0 mg sarolaner / 0.96 mg moxidectin / 200 mg pyrantel (as pamoate salt)
72.0 mg sarolaner / 1.44 mg moxidectin / 300 mg pyrantel (as pamoate salt)

H. How Supplied

SimparicaTRIO® is available in six sizes, in color-coded packages of 1, 3, or 6 flavored chewable tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

SimparicaTRIO® 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/Class

Dogs

M. Indication

SimparicaTRIO® 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. SimparicaTRIO® kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment and prevention of flea infestations, 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. SimparicaTRIO® 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 treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations 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 SimparicaTRIO® against *Haemaphysalis longicornis* was demonstrated in two well-controlled laboratory studies, described below. Both studies included three groups of dogs (control, Simparica®, and SimparicaTRIO®), but only the results of the control and SimparicaTRIO® groups are presented. These studies demonstrated that SimparicaTRIO® is effective for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater.

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 the New Animal Drug Application (NADA) 141-521 dated February 27, 2020, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study A162C-US-22-C80

   Title: Laboratory Efficacy of Simparica® and SimparicaTRIO® Against Induced Infestations of *Haemaphysalis longicornis* on Dogs. (Study No. A162C-US-22-C80)

   Study Dates: February 7, 2023 to November 6, 2023

   Study Location: Waverly, NY

   Study Design:

   Objective: To confirm the effectiveness of a single oral administration of SimparicaTRIO® against induced infestations of *H. longicornis* on dogs for one month.

   Study Animals: Twenty Beagle dogs (10 males and 10 females), 10 to 15 months of age, and 5.8 to 9.9 kg body weight.

   Experimental Design: This study was a negative-controlled, masked, randomized complete block study design. Dogs were randomly assigned to the control group (10 dogs) or the SimparicaTRIO® group (10 dogs). Each dog was sedated with dexmedetomidine hydrochloride administered intramuscularly and then infested with approximately 50 viable, unfed, adult *H. longicornis* ticks on Days -2, 7, 14,

21, and 30. Ticks were counted and removed on Days 2, 9, 16, 23, and 32. The study was conducted in accordance with Good Clinical Practice (GCP) guidance.

Table II.1. Treatment Groups (Study No. A162C-US-22-C80)

Treatment Group	Treatment	Dosage	Day of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Counts
T01	Control*	N/A	Day 0	10	Days -2, 7, 14, 21, 30	Days 2, 9, 16, 23, 32
T02	SimparicaTRIO® (sarolaner + moxidectin + pyrantel (as pamoate salt))	1.2 mg/kg + 24 µg/kg + 5 mg/kg	Day 0	10	Days -2, 7, 14, 21, 30	Days 2, 9, 16, 23, 32

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

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

Measurements and Observations: Ticks were removed, and numbers of live and dead ticks were counted at each tick count. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted twice daily.

Statistical Methods: For live tick counts, percent effectiveness against control was calculated based on arithmetic means using the formula [(C - T)/C] x 100, where C = arithmetic mean calculated from the least squares means of live tick counts for the control group and T = arithmetic mean calculated from the least squares means of live tick counts for the treated group. Live tick counts for treated and control dogs were compared using a mixed linear model with treatment group as a fixed effect, and error and block as random effects at each time point. Testing was two-sided at the 5% significance level. For dead tick counts, the arithmetic means were calculated by treatment group and timepoint.

Results: Control dogs maintained adequate tick infestations throughout the study with at least six of the ten dogs having 12 or more live ticks at each tick count.

There were no live ticks on any dog administered SimparicaTRIO® for 32 days after dosing. These dogs had a 100% reduction in live tick counts 48 hours after dose administration and 48 hours after weekly re-infestations for 32 days (Table II.2).

Mean live tick counts for the dogs administered SimparicaTRIO® were significantly different ($P<0.0001$) and numerically lower than for the control dogs on all days after dosing.

Table II.2. Arithmetic Mean Live Tick Count and Percent Effectiveness

Day of Tick Count	Control Group Arithmetic Mean Live Tick Count	SimparicaTRIO® Arithmetic Mean Live Tick Count	Percent Effectiveness
2	13.1	0.0	100%
9	15.0	0.0	100%
16	31.4	0.0	100%
23	29.7	0.0	100%
32	27.1	0.0	100%

Mean dead tick counts for the dogs administered SimparicaTRIO® were higher than for the control dogs on all tick count days after dosing.

Table II.3. Arithmetic Mean Dead Tick Count

Day of Tick Count	Control Group Arithmetic Mean Dead Tick Count	SimparicaTRIO® Arithmetic Mean Dead Tick Count
2	0.1	0.7
9	0.1	2.2
16	0.1	1.4
23	0.5	3.3
32	0.0	2.1

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

Conclusion: This study demonstrated the effectiveness of SimparicaTRIO® for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* for one month when assessed at 48 hours after drug administration or infestation.

2. Laboratory Dose Confirmation Study A162C-ZA-22-C81

Title: Laboratory Efficacy of Simparica® and SimparicaTRIO® Against Induced Infestations of *Haemaphysalis longicornis* on Dogs. (Study No. A162C-ZA-22-C81)

Study Dates: March 27, 2023 to October 31, 2023

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the effectiveness of a single oral administration of SimparicaTRIO® against induced tick infestations of *H. longicornis* on dogs for one month.

Study Animals: Twenty Beagle and mongrel dogs (10 males and 10 females), 7 to 79 months of age, and 11 to 21.4 kg body weight.

Experimental Design: This study was a negative-controlled, masked, randomized complete block study design. Dogs were randomly assigned to the control group

(10 dogs) or the SimparicaTRIO® group (10 dogs). Each dog was sedated with dexmedetomidine hydrochloride intramuscularly and then infested with approximately 50 viable, unfed, adult *H. longicornis* ticks on Days -2, 7, 14, 21, and 30. Ticks were counted and removed on Days 2, 9, 16, 23, and 32. The study was conducted in accordance with Good Clinical Practice (GCP) guidance.

Table II.4. Treatment Groups (Study No. A162C-ZA-22-C81)

Treatment Group	Treatment	Dosage	Day of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Counts
T01	Control*	N/A	Day 0	10	Days -2, 7, 14, 21, and 30	Days 2, 9, 16, 23, and 32
T02	SimparicaTRIO® (sarolaner + moxidectin + pyrantel (as pamoate salt))	1.2 mg/kg + 24 µg/kg + 5 mg/kg	Day 0	10	Days -2, 7, 14, 21, and 30	Days 2, 9, 16, 23, and 32

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

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

Measurements and Observations: Ticks were removed, and numbers of live and dead ticks were counted at each tick count. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted twice daily.

Statistical Methods: For live tick counts, percent effectiveness against control was calculated based on arithmetic means using the formula [(C-T)/C] x 100, where C = arithmetic mean calculated from the least squares means of live tick counts for the control group and T = arithmetic mean calculated from the least squares means of live tick counts for the treated group. Live tick counts for treated and control dogs were compared using a mixed linear model with treatment group as a fixed effect, and room, block within room and error as random effects at each time point. Testing was two-sided at the 5% significance level. For dead tick counts, the arithmetic means were calculated by treatment group and timepoint.

Results: Control dogs maintained adequate tick infestations throughout the study with at least six of the ten dogs having 12 or more live ticks at each tick count.

Dogs administered SimparicaTRIO® had a 100% reduction in live tick counts 48 hours after treatment of the existing infestation, and ≥99.6% reduction in live tick counts 48 hours after weekly re-infestations for 32 days (Table II.5).

Mean live tick counts for the dogs administered SimparicaTRIO® were significantly different (P<0.0001) and numerically lower than for the control dogs on all days after dosing.

Table II.5. Arithmetic Mean Live Tick Count and Percent Effectiveness

Day of Tick Count	Control Group Arithmetic Mean Live Tick Count	SimparicaTRIO® Arithmetic Mean Live Tick Count	Percent Effectiveness
2	31.5	0.0	100%
9	24.2	0.0	100%
16	24.8	0.1	99.6%
23	30.3	0.0	100%
32	29.1	0.1	99.7%

Mean dead tick counts for the dogs administered SimparicaTRIO® were higher than for the control dogs on all tick count days after dosing.

Table II.6. Arithmetic Mean Dead Tick Count

Day of Tick Count	Control Group Arithmetic Mean Dead Tick Count	SimparicaTRIO® Arithmetic Mean Dead Tick Count
2	0.2	8.2
9	0.0	3.0
16	0.1	2.1
23	0.0	1.3
32	0.0	1.7

Adverse Reactions: One dog in the SimparicaTRIO® group had a seizure on Day 16 described as mild twitching and foaming at the mouth.

Conclusion: This study demonstrated the effectiveness of SimparicaTRIO® for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* for one month when assessed at 48 hours after drug administration or infestation.

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 SimparicaTRIO®:

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 SimparicaTRIO®, 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 SimparicaTRIO® 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 treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations 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.