Date of Approval: December 12, 2016

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-452

SIMPARICA™

sarolaner

Chewable tablets

Dogs

The effect of this supplement is to provide for the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or greater.

Sponsored by:

Zoetis Inc.

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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. 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

Rx

J. Dosage Regimen

0.91 mg/lb (2 mg/kg) body weight, once per month

K. Route of Administration

Oral

L. Species/Class

Dog

M. Indication

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.

N. Effect of Supplement

The effect of this supplement is to provide for the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or greater.

II. EFFECTIVENESS

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. Dose Confirmation Study A166C-US-12-108:

   Title: Dose Confirmation of Sarolaner Administered Orally Against Induced Infestations of *Ixodes scapularis* on Dogs

   Study Dates: March 20, 2013, through August 27, 2013

   Location of Study: Greenbrier, AR

   Study Design:

   Study Objective*:* Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Ixodes scapularis* for up to 35 days on dogs.

   Study Animals: 16 Beagle and mixed breed dogs (8 male and 8 female), 15 - 78 months of age, weighing between 7.1 – 12.4 kg.

Treatment Groups:

Table 1. Treatment groups for Study A166C-US-12-108

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle Control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

Drug Administration: All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

Measurements and Observations: Each dog was infested with approximately 50 unfed adult *I. scapularis* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

Statistical Methods*:*

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

Effectiveness for the control indication was determined on the basis of the percent reduction in live tick counts in the treated group compared to the control group.

Results:

The sarolaner-treated group had a 100% reduction in initial live tick counts 48 hours after treatment, and 100% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$, Table 2). Total dead tick counts were significantly increased ($P\leq0.0001$, Table 3) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 2: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *I. scapularis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	24.7	0.0	100
7	28.4	0.0	100
14	24.8	0.0	100
21	17.4	0.0	100
28	20.9	0.0	100
35	25.8	0.0	100

Table 3: Geometric mean dead tick counts of sarolaner for the treatment of induced *I. scapularis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	7.4
7	0.0	7.8
14	0.0	14.3
21	0.0	14.0
28	0.0	8.8
35	0.0	10.3

Adverse Reactions: No adverse reactions were reported in this study

Conclusions: Sarolaner was effective against adult *I. scapularis* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *I. scapularis*, respectively.

2. Dose Confirmation Study A166C-US-15-608

Title: Dose Confirmation of Sarolaner Administered Orally Against Induced Infestations of *Ixodes scapularis* on Dogs

Study Dates: November 9, 2015, through April 12, 2016

Location of Study: Turlock, CA

Study Design:

Study Objective*:* Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Ixodes scapularis* for up to 35 days on dogs.

Study Animals: 20 Beagle dogs (10 male and 10 female), 62 - 116 months of age, weighing between 8.3 – 15.8 kg

Treatment Groups:

Table 4. Treatment groups for Study A166C-US-15-608

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle Control	Day 0	10	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	10	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

Drug Administration: All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

Measurements and Observations: Each dog was infested with approximately 50 unfed adult *I. scapularis* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

Effectiveness for the control indication was determined on the basis of the percent reduction in live tick counts in the treated group compared to the control group.

Results:

The sarolaner-treated group had a 99.4% reduction in initial live tick counts 48 hours after treatment, and ≥99.6% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$, Table 5). Total dead tick counts were significantly increased ($P<0.0001$, Table 6) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 5: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *I. scapularis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	31.8	0.2	99.4
7	28.9	0.1	99.6
14	27.1	0.0	100
21	26.5	0.1	99.7
28	26.0	0.1	99.7
35	23.9	0.0	100

Table 6: Geometric mean dead tick counts of sarolaner for the treatment of induced *I. scapularis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Live Tick Count
2	0.0	5.8
7	0.0	7.7
14	0.0	7.9
21	0.0	11.1
28	0.0	9.9
35	0.0	8.9

Adverse Reactions: No adverse reactions were reported in this study.

Conclusions: Sarolaner was effective against adult *I. scapularis* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *I. scapularis*, respectively.

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 and 21 CFR part 514. The data demonstrate that SIMPARICA™ is effective for the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or greater.

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 Federal Food, Drug, and Cosmetic Act because the supplemental approval included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or greater.

C. Supplemental Applications

This supplemental NADA did not require 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 Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.