Date of Approval: February 23, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-406

NEXGARD

Afoxolaner

Chewable Tablet

Dogs

The effect of the supplement is to provide for the treatment and control of Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

Sponsored by:

Merial, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-406

B. Sponsor

Merial, Inc.
3239 Satellite Blvd., Bldg. 500
Duluth, GA 30096-4640

Drug Labeler Code: 050604

C. Proprietary Name

NEXGARD

D. Established Name

Afoxolaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable contains 11.3 mg, 28.3 mg, 68 mg, or 136 mg afoxolaner.

H. How Supplied

NEXGARD is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68, or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

I. Dispensing Status

Rx

J. Dosage Regimen

NEXGARD is given orally, once a month at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	Administer the appropriate combination of chewables

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

NEXGARD kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of Black-legged tick (*Ixodes scapularis*), American Dog tick (*Dermacentor variabilis*), Lone Star tick (*Amblyomma americanum*) and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

N. Effect of Supplement

The effect of the supplement is to provide for the treatment and control of Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved 1.14 mg/lb (2.5 mg/kg) dose, given orally once a month. The Freedom of Information (FOI) Summary for the original approval of NADA 141-406, dated September 14, 2013, contains dosage characterization information for dogs.

B. Substantial Evidence

1. For the Treatment and Control of Tick Infestations:

a. Laboratory Dose Confirmation Study PR&D 0233601

Title: Efficacy of ML-3,663,925 for the Treatment and Prevention of Infestation against Induced Infestations of *Rhipicephalus sanguineus* and *Dermacentor reticulatus* Ticks on Dogs after a Single Oral Dose Administered to achieve at Least 2.5 mg/kg

(1) Location:

ClinVet International Pty Ltd.
Bloemfontein, South Africa

(2) Study Design:

(a) Objective:

Confirm the effectiveness of a single oral dose (at least 2.5 mg/kg) of afoxolaner for the treatment and control of induced infestations of adult stages of R. sanguineus on dogs.

(b) Study Animals:

16 Beagle dogs (7 males, 9 females), ≥ 6 months of age, weighing between 11.0-18.4 kg

(c) Treatment Groups:

Table 1: Treatment groups for Study PR&D 0233601.

Treatment Group	Dose	Treatment	Frequency/ Duration	Number and Gender of Dogs
1	0 mg/kg	Control (untreated)	Once on Day 0	8 (3 M, 5 F)
2	2.5 mg/kg	NEXGARD	Once on Day 0	8 (4 M, 4 F)

(d) Drug Administration:

All treatments were administered orally. Food was removed overnight on the day prior to dosing. On Day 0, dogs were fed 4 hours after treatment administration.

(e) Measurements and Observations:

Physical examinations were conducted on Day -7. On Days -2, 7, 14, 21, 28, and 35 each dog was infested with 50 ±5 unfed adult ticks *(R. sanguineus).* Twenty-four hours after infestation, dead ticks were counted from collection pans beneath each animal cage. At 48-hours post-treatment on Day 0 and at 48-hours post-infestation on the remaining days, live and dead ticks were removed and counted from individual animals, and dead ticks were counted from collection pans. For the Day -2 infestation, ticks found dead in the collection pans were counted at 48 and 72 hours post-infestation. General health observations were conducted at least once daily for all dogs. On Day 0, post-dosing clinical observations were conducted hourly for the first four hours post-dose for evidence of vomiting or other adverse events.

(f) 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. For dead tick counts, the formula was reversed as [(T - C)/T] x 100. 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.

(3) Results:

NEXGARD was ≥98.6% effective against live *R. sanguineus* ticks at 48 hours post-infestation through Day 30 (Table 2). Live tick counts were significantly reduced ($P < 0.001$) following each of the infestation time points in comparison with the control group. Total dead tick counts were significantly increased ($P \leq 0.002$, 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 NEXGARD for the control of induced *R. sanguineus* infestations of dogs, 48 hours after infestation.

Days After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean	Percent Effectiveness at 48 Hours Post-infestation
2	27.2	0.0	100.0
9	27.8	0.4	98.7
16	27.6	0.2	99.3
23	26.5	0.4	98.6
30	26.2	0.2	99.3
37	28.5	0.5	98.3

Table 3: Geometric mean dead tick counts of NEXGARD for the treatment of induced *R. sanguineus* infestations of dogs, 48 hours after infestation.

Days After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean
2	0.1	18.5
9	0.8	13.7
16	1.0	17.1
23	1.4	14.8
30	1.2	8.3
37	0.6	10.1

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD was >98% effective against adult *R. sanguineus*, when measured 48 hours after infestation, for 30 days. The increased number of dead ticks and the reduction of live ticks support the treatment and control indications for *R. sanguineus*, respectively.

b. Laboratory Dose Confirmation Study PR&D 0233004

Title: Efficacy of ML-3,663,925 Against Induced Infestations of Adult *Rhipicephalus sanguineus* on Dogs after a Single Oral Dose Administered to Achieve at Least 2.5 mg/kg

(1) Location:

TRS Labs, Inc.
Athens, GA

(2) Study Design:

(a) Objective:

Confirm the effectiveness of a single oral dose (at least 2.5 mg/kg) of afoxolaner for the treatment and control of induced infestations of adult stages of adult *R. sanguineus* on dogs.

(b) Study Animals:

20 Beagle dogs (8 males, 12 females), 6.0 to 7.0 months of age, weighing 4.6 - 7.3 kg

(c) Treatment Groups:

Table 4: Treatment groups for Study PR&D 0233004.

Treatment Group	Dose	Treatment	Frequency/ Duration	Number and Gender of Dogs
1	0 mg/kg	Control (untreated)	Once on Day 0	10 (4 M, 6 F)
2	2.5 mg/kg	NEXGARD	Once on Day 0	10 (4 M, 6 F)

(d) Drug Administration:

All treatments were administered orally. Food was removed overnight on the day prior to dosing. On Day 0, dogs were fed 4 hours after treatment administration.

(e) Measurements and Observations:

Physical examinations were conducted on Day -12. On Days -7, -1, 7, 14, 21, 28, and 35 each dog was infested with 50 ±5 unfed adult ticks (*R. sanguineus*). Twenty-four hours after infestation, dead ticks were counted from collection pans beneath each animal cage. At 48-hours post-treatment on Day 0 and at 48-hours post-infestation on the remaining days, live and dead ticks were removed and counted from individual animals, and dead ticks were counted from collection pans. For the Day -1 infestation, ticks found dead in the collection pans were counted at 48 and 72 hours post-infestation. General health observations were conducted at least once daily for all dogs. On Day 0, post-dosing clinical observations were conducted hourly for the first four hours post-dose for evidence of vomiting or other adverse events.

(f) 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. For dead tick counts, the formula was reversed as [(T - C)/T] x 100. 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.

(3) Results:

NEXGARD was ≥83.9% effective against live *R. sanguineus* ticks at 48 hours post-infestation through Day 30 (Table 5). Live tick counts were significantly reduced ($P \leq 0.001$) following each of the infestation time points in comparison with the control group. Total dead tick counts were significantly increased ($P < 0.004$, 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 in Table 5.

Table 5: Geometric mean live tick counts and percent effectiveness of NEXGARD for the control of induced *R. sanguineus* infestations of dogs, 48 hours after infestation.

Days After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean	Percent Effectiveness at 48 Hours Post-infestation
2	31.2	0.1	99.8
9	26.3	0.1	99.7
16	34.5	0.3	99.2
23	28.5	1.2	96.0
30	30.9	5.0	83.9
37	20.2	6.0	70.2

Table 6: Geometric mean dead tick counts of NEXGARD for the treatment of induced *R. sanguineus* infestations of dogs, 48 hours after infestation.

Days After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean
2	0.1	28.7
9	0.1	18.9
16	0.6	21.4
23	0.8	16.4
30	0.2	8.8
37	0.8	3.8

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD failed to demonstrate adequate ($\geq$ 90%) effectiveness for the control of *R. sanguineus* when measured 48 hours after infestation, for 30 days.

c. Laboratory Dose Confirmation Study PR&D 0233005

Title: Efficacy of ML-3,663,925 Against Induced Infestations of Adult *Rhipicephalus sanguineus* on Dogs after a Single Oral Dose Administered to Achieve at Least 2.5 mg/kg

(1) Location:

Merial, Inc.
Colbert, GA

(2) Study Design:

(a) Objective:

Confirm the effectiveness of a single oral dose (at least 2.5 mg/kg) of afoxolaner for the treatment and control of induced infestations of adult stages of *R. sanguineus* on dogs.

(b) Study Animals:

20 Beagle dogs (11 males, 9 females), 6.4 to 7.4 months of age, weighing between 6.7 – 9.3 kg

(c) Treatment Groups:

Table 7: Treatment groups for Study PR&D 0233005.

Treatment Group	Dose	Treatment	Frequency/ Duration	Number and Gender of Dogs
1	0 mg/kg	Control (untreated)	Once on Day 0	10 (4 M, 6 F)
2	2.5 mg/kg	NEXGARD	Once on Day 0	10 (7 M, 3 F)

(d) Drug Administration:

All treatments were administered orally. Food was removed overnight on the day prior to dosing. On Day 0, dogs were fed 4 hours after treatment administration.

(e) Measurements and Observations:

Physical examinations were conducted on Day -8. On Days -1, 7, 14, 21, 28 and 35, each dog was infested with 50 ± 5 unfed adult ticks (*R. sanguineus*) ticks. Twenty-four hours after infestation, dead ticks were counted from collection pans beneath each animal cage. At 48-hours post-treatment on Day 0 and 48-hours post-infestation on the remaining days, live and dead ticks were removed and counted from individual animals, and dead ticks were counted from collection pans. For the Day -1 infestation, ticks found dead in the collection pans were counted at 48- and 72-hours post-infestation. General health observations were conducted at least once daily for all dogs, with the exception of Day 33. On Day 0, post-dosing clinical observations were conducted hourly for the first four hours post-dose for evidence of vomiting or other adverse events.

(f) 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. For dead tick counts, the formula was reversed as [(T - C)/T] x 100. 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 tick counts in the treated group compared to the control group.

(3) Results:

NEXGARD was ≥ 93.5% effective against live *R. sanguineus* ticks at 48 hours post-infestation through Day 30 (Table 8). Live tick counts were significantly reduced ($P < 0.001$) following each of the infestation time points in comparison with the control group. Total dead tick counts were significantly increased ($P < 0.001$, Table 9) 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 8: Geometric mean live tick counts and percent effectiveness of NEXGARD for the control of induced *R. sanguineus* infestations of dogs, 48 hours after infestation.

Days After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean	Percent Effectiveness at 48 hours Post-infestation
2	29.7	0.0	100.0
9	27.2	0.1	99.7
16	24.9	0.2	99.2
23	19.4	0.1	99.2
30	20.6	1.3	93.5
37	19.7	1.6	92.4

Table 9: Geometric mean dead tick counts of NEXGARD for the treatment of induced *R. sanguineus* infestations of dogs, 48 hours after infestation.

Days After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean
2	0.0	30.0
9	0.2	24.5
16	0.3	21.9
23	0.3	18.8
30	0.7	14.2
37	0.2	7.4

(4) Adverse Reactions:

One dog had diarrhea within one day post-treatment; this dog had diarrhea one day prior to treatment as well. A second dog had diarrhea 12 and 24 days post-treatment.

(5) Conclusions:

NEXGARD was ≥ 93.5% effective against adult *R. sanguineus*, when measured 48 hours after infestation, for 30 days. The increased number of dead ticks and the reduction of live ticks support the treatment and control indications for *R. sanguineus*, respectively.

d. Overall Conclusion for *R. sanguineus:*

Although Study PR&D 0233004 failed to demonstrate > 90% effectiveness at Day 30, when combined with Study 0233601 and Study 0233005, the average effectiveness is > 90% (92.2%). Therefore, the combined data demonstrates that NEXGARD is effective for the treatment and control of *R. sanguineus* infestations for 30 days when assessed at 48 hours after drug administration or infestation.

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 141-406 dated September 14, 2013, contains a summary of target animal safety studies for species, dosage, or other applicable information.

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 NEXGARD:

Warnings: Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

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 NEXGARD, when used according to the label, is safe and effective for the treatment and control of Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

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 NEXGARD 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 Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

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.