Date of Approval: May 15, 2014

# 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 Black-legged tick (*Ixodes scapularis*) and Lone Star tick (*Amblyomma americanum*) 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 Ltd.

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# I. GENERAL INFORMATION

## A. File Number

NADA 141-406

## B. Sponsor

Merial Ltd.
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*), and Lone Star tick (*Amblyomma americanum*) 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 Black-legged tick (*Ixodes scapularis*) and Lone Star tick (*Amblyomma americanum*) 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 0233301

Title: Efficacy of ML-3,663,925 Against Induced Infestations of Adult *Ixodes scapularis* 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 *I. scapularis* on dogs.

(b) Study Animals:

16 Beagle dogs (8 males, 8 females), 6.3 to 7.5 months of age, weighing between 5.2 – 8.7 kg

(c) Treatment Groups:

Table 1: Treatment groups for Study PR&D 0233301.

| Treatment Group | Dose | Treatment | Frequency/ Duration | Number and Gender of Dogs |
|---|---|---|---|---|
| 1 | 0 mg/kg | Control (untreated) | Once on Study Day 0 | 8 (5 M, 3 F) |
| 2 | 2.5 mg/kg | NEXGARD | Once on Study Day 0 | 8 (3 M, 5 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 -5. On Days -1, 7, 14, 21, 28, and 35 each dog was infested with 50 ±5 unfed adult ticks *(I. scapularis).* Twenty-four hours after infestation, dead ticks were counted from collection pans beneath each animal cage. At 48-hours post-infestation, 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 random effects.

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 ≥94.2% effective against live *I. scapularis* ticks at 48 hours post-infestation through Day 30 (Table 2). Live tick counts were significantly reduced ($P \leq 0.002$) following each of the infestation time points in comparison with the control group. Total dead tick counts were significantly increased ($P \leq 0.001$, 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 in Table 2. On Day 7, two dogs were infested with tick populations that were considered to have reduced vitality. This compromised their tick infestations on Day 7 only.

Table 2: Geometric mean live tick counts and percent effectiveness of NEXGARD for the control of induced *I. scapularis* 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 | 21.1 | 0.3 | 98.4 |
| 16 | 20.9 | 0.2 | 99.1 |
| 23 | 20.9 | 0.1 | 99.6 |
| 30 | 14.2 | 0.8 | 94.2 |
| 37 | 20.0 | 2.0 | 89.9 |

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

| Days after Treatment | Control Group Geometric Mean | NEXGARD Group Geometric Mean |
|---|---|---|
| 2 | 0.5 | 19.6 |
| 16 | 4.3 | 23.1 |
| 23 | 2.9 | 19.5 |
| 30 | 7.7 | 24.1 |
| 37 | 5.3 | 21.5 |

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD was ≥94.2% effective against adult *I. scapularis*, 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 *I. scapularis*, respectively.

b. Laboratory Dose Confirmation Study PR&D 0233303

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

(1) Location:

Merial Limited
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 *I. scapularis* on dogs.

(b) Study Animals:

20 Beagle dogs (10 males, 10 females), 9.8 to 14.2 months of age, weighing between 6.1 – 13.7 kg.

(c) Treatment Groups:

Table 4: Treatment groups for Study PR&D 0233303.

| Treatment Group | Dose | Treatment | Frequency / Duration | Number and Gender of Dogs |
|---|---|---|---|---|
| 1 | 0 mg/kg | Control (untreated) | Once on Study Day 0 | 10 (6 M, 4 F) |
| 2 | 2.5 mg/kg | NEXGARD | Once on Study 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 -21. On Days -21, -14, -1, 7, 14, 21, 28 and 35, each dog was infested with 50 ±5 unfed adult ticks (*I. scapularis*). Twenty-four hours after infestation, dead ticks were counted from collection pans beneath each animal cage. At 48-hours post-infestation, 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 random effects.

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 ≥98.0% effective against live *I. scapularis* ticks at 48 hours post-infestation through Day 30 (Table 5). 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 ($P \leq 0.007$, 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 *I. scapularis* 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 | 19.7 | 0.0 | 100.0 |
| 9 | 15.7 | 0.2 | 98.5 |
| 16 | 12.7 | 0.2 | 98.5 |
| 30 | 17.4 | 0.3 | 98.0 |
| 37 | 15.0 | 0.5 | 96.6 |

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

| Days after Treatment | Control Group Geometric Mean | NEXGARD Group Geometric Mean |
|---|---|---|
| 2 | 1.4 | 20.2 |
| 9 | 8.6 | 23.7 |
| 16 | 5.5 | 19.6 |
| 30 | 3.4 | 12.4 |
| 37 | 4.9 | 12.6 |

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD was ≥98.0% effective against adult *I. scapularis*, 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 *I. scapularis*, respectively.

c. Laboratory Dose Confirmation Study PR&D 0233106

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

(1) Location:

Merial Limited
Fulton, MO

(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 *A. americanum* on dogs.

(b) Study Animals:

20 Beagle dogs (12 male, 8 females), 26.8 to 46.2 months, weighing between 9.0 - 13.3 kg.

(c) Treatment groups:

Table 7: Treatment groups for Study PR&D 0233106.

| Treatment Group | Dose | Treatment | Frequency/ Duration | Number and Gender of Dogs |
|---|---|---|---|---|
| 1 | 0 mg/kg | Control (untreated) | NA | 10 (4 M, 6 F) |
| 2 | 2.5 mg/kg | NEXGARD | Once on Study Day 0 | 10 (8 M, 2 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 -11. On Days -7, -1, 7, 14, 21, 28 and 35, each dog was infested with 50 ±5 unfed adult ticks (*A. americanum*). Twenty-four hours after infestation, dead ticks were counted from the collection pans beneath each animal cage. At 72 hours post-infestation, live and dead ticks were removed and counted from individual animals, and dead ticks were counted from collection pans. 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 random effects.

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 ≥98.9% effective against live *A. americanum* ticks at 72 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 ($P \leq 0.001$, 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 in Table 8.

Table 8: Geometric mean live tick counts and percent effectiveness of NEXGARD for the control of induced *A. americanum* infestations of dogs, 72 hours after infestation.

| Days after Treatment | Control Group Geometric Mean | NEXGARD Group Geometric Mean | Percent Effectiveness at 72 hours Post-infestation |
|---|---|---|---|
| 2 | 23.3 | 0.0 | 100.0 |
| 10 | 13.4 | 0.0 | 100.0 |
| 17 | 14.6 | 0.0 | 100.0 |
| 24 | 17.5 | 0.0 | 100.0 |
| 31 | 15.3 | 0.2 | 98.9 |
| 38 | 16.2 | 0.6 | 96.4 |

Table 9: Geometric mean dead tick counts of NEXGARD for the treatment of induced *A. americanum* infestations of dogs, 72 hours after infestation.

| Days after Treatment | Control Group Geometric Mean | NEXGARD Group Geometric Mean |
|---|---|---|
| 2 | 1.5 | 18.6 |
| 10 | 3.6 | 15.5 |
| 17 | 2.3 | 14.6 |
| 24 | 1.4 | 14.6 |
| 31 | 1.4 | 14.3 |
| 38 | 3.4 | 16.4 |

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD was ≥98.9% effective against adult *A. americanum*, when measured 72 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 *A. americanum*, respectively.

d. Laboratory Dose Confirmation Study PR&D 0233109

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

(1) Location:

Merial Limited
Fulton, MO

(2) Study Design:

(a) Objective:

Confirm the effectiveness of ML-3,663,925 for the treatment and control against induced infestations of adult stages of *Amblyomma americanum* on dogs after a single oral dose administered to achieve at least 2.5 mg/kg.

(b) Study Animals:

20 Beagle dogs (8 male, 12 females), 14.8 to 16.8 months, weighing between 7.1 kg to 12.8 kg.

(c) Treatment groups:

Table 10: Treatment groups for Study PR&D 0233109.

| Treatment Group | Dose | Treatment | Frequency/ Duration | Number and Gender of Dogs |
|---|---|---|---|---|
| 1 | 0 mg/kg | Control (untreated) | NA | 10 (4 M, 6 F) |
| 2 | 2.5 mg/kg | NEXGARD | Once on Study 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, with the exception of 2 dogs. On Day 0, dogs were fed 4 hours after treatment administration.

(e) Measurements and Observations:

Physical examinations were conducted on Day -8. On Days -7, -1, 7, 14, 21, 28 and 35, each dog was infested with 50 ±5 unfed adult ticks (*A. americanum*). Twenty-four and 48 hours after infestation, dead ticks were counted and removed from the collection pans beneath each animal cage. At 72 hours post-infestation, live and dead ticks were removed and counted from individual animals, and dead ticks were counted from collection pans. 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 random effects.

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 ≥97.8% effective against live *A. americanum* ticks at 72 hours post-infestation through Day 30 (Table 11). 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 ($P\leq0.018$, Table 12) 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 11.

Table 11: Geometric mean live tick counts and percent effectiveness of NEXGARD for the control of induced *A. americanum* infestations of dogs, 72 hours after infestation.

| Days after Treatment | Control Group Geometric Mean | NEXGARD Group Geometric Mean | Percent Effectiveness at 72 hours Post-infestation |
|---|---|---|---|
| 2 | 23.5 | 0.0 | 100.0 |
| 10 | 23.5 | 0.1 | 99.7 |
| 17 | 13.8 | 0.0 | 100.0 |
| 24 | 19.1 | 0.0 | 100.0 |
| 31 | 14.0 | 0.3 | 97.8 |
| 38 | 21.2 | 0.1 | 99.5 |

Table 12: Geometric mean dead tick counts of NEXGARD for the treatment of induced *A. americanum* infestations of dogs, 72 hours after infestation.

| Days after Treatment | Control Group Geometric Mean | NEXGARD Group Geometric Mean |
|---|---|---|
| 2 | 1.2 | 20.0 |
| 10 | 2.2 | 14.6 |
| 17 | 1.6 | 9.8 |
| 24 | 1.5 | 16.2 |
| 31 | 3.6 | 9.4 |
| 38 | 1.7 | 17.8 |

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD was ≥97.8% effective against adult *A. americanum*, when measured 72 hours after infestation, for 30 days. The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *A. americanum*, 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 141-406 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 Black-legged tick (*Ixodes scapularis*) and Lone Star tick (*Amblyomma americanum*) 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 Black-legged tick (*Ixodes scapularis*) and Lone Star tick (*Amblyomma americanum*) 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.