Date of Approval: July 13, 2018

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-406

NexGard®

afoxolaner

Chewable Tablet

Dogs

This supplement provides for the addition of the indication for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Sponsored by:

Merial, Inc.

Table of Contents

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. Product 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 one, three, or six 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. **NexGard® 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 *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

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

The effectiveness of NexGard® was demonstrated in two well-controlled laboratory studies described below. No adverse reactions were reported in any of the twenty dogs administered the labeled dose. These studies demonstrated that NexGard® is effective to prevent transmission of *Borrelia burgdorferi* by killing *Ixodes scapularis* ticks on the dogs before they could transmit the infection. The supplemental approval of NADA 141-406, dated May 15, 2014, demonstrated that NexGard® is effective against *I. scapularis* ticks for 30 days.

1. Laboratory Effectiveness Study

Title: A Study to Evaluate the Ability of a Single Treatment with NexGard® to Prevent the Transmission of *Borrelia burgdorferi* to Dogs from Infected *Ixodes scapularis;* Study number 0377501

Study Dates: January 19, 2017 to September 25, 2017

Study Location: Colbert, GA, USA

Study Design:

Study Objective: To evaluate the ability of a single treatment of NexGard® to prevent the transmission of *Borrelia burgdorferi* to dogs following an induced infestation with naturally infected wild-caught *Ixodes scapularis*. This study was conducted in accordance with Good Clinical Practices.

Study Animals: 20 Beagle dogs (10 males, 10 females), 6.7-8.0 months of age, weighing between 5.8-9.2 kg.

Treatment Groups: This was a masked study using a randomized block design.

Table II.1. Treatment Groups

Treatment Group	Minimum Dose	Treatment	Treatment Day	Number and Gender of Dogs
1	0 mg/kg	Control (untreated)	Day 0	10 (5 M, 5 F)
2	2.5 mg/kg	NexGard®	Day 0	10 (5 M, 5 F)

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

Measurements and Observations: The primary endpoints for effectiveness were live tick counts and infection with *B. burgdorferi* defined by serology tests and polymerase chain reaction (PCR) tests of skin biopsies. The Lyme Quant C6® and SNAP® 4Dx® (IDEXX laboratories) tests were used to determine the *B. burgdorferi* infection status of the dogs, as evidenced by the presence of C6 *B. burgdorferi* antibody after tick infestations. Both tests were

conducted on samples collected prior to treatment and tick infestations (Days -4 and 27, respectively) and thereafter (Days 48, 62, 76, 90, and 102). Additionally, the dogs were tested for the presence of *B. burgdorferi* DNA by PCR testing of 4 skin biopsies per dog collected on Day 104 from the heaviest sites of tick attachment, as marked on Day 33. On Day 28, all dogs were infested with 50±5 adult, unfed, wild-caught *I. scapularis* ticks. The ticks had a *B. burgdorferi* infection rate of 63.1%. The ticks were counted and removed by thorough combing on Day 33. General health observations were conducted at least once daily for all dogs.

Statistical Methods:

Serology: A dog was determined to be infected with *B. burgdorferi* if a positive result was obtained on either the SNAP® 4Dx® test or the Lyme Quant C6® tests (titer ≥ 30 U/mL) at any sampling time point, or a positive PCR test result was obtained from any of the four skin biopsies. For a dog to be considered negative for *B. burgdorferi* infection, a negative result must be obtained for both serology tests at all sampling time points and for the PCR tests at all skin biopsies. The proportion of animals positive for *B. burgdorferi* in the NexGard® group was compared to the proportion of positive animals in the control group using Fisher's Exact test.

Tick Counts: The percent effectiveness of the NexGard® against ticks was calculated using the formula [(C-T)/C] x 100, where C and T are the Least Squares means of the tick counts estimated from the statistical model on the dogs in the control and NexGard®-treated groups, respectively. The raw tick counts were analyzed using a mixed model analysis of variance with treatment group as a fixed effect and the allocation blocks as a random effect.

Results: All dogs were seronegative for *B. burgdorferi* before treatment and tick infestations. All 10 dogs treated with NexGard® remained seronegative for *B. burgdorferi* antibody by all tests throughout the study. The proportion of control dogs seropositive for Lyme Quant C6® *B. burgdorferi* antibody increased during the study until all 10 control dogs were seropositive for *B. burgdorferi* antibody on Day 62. All control dogs were seropositive by SNAP® 4Dx® and Lyme Quant C6® tests on Days 90 and 102.

All control dogs were positive for *B. burgdorferi* on PCR testing in at least 3 of the 4 skin biopsies. All dogs treated with NexGard® were negative for *B. burgdorferi* on the PCR testing of all skin biopsies.

Overall, all 10 dogs treated with NexGard® were negative for *B. burgdorferi* throughout the study, and all the 10 control dogs were positive for *B. burgdorferi* by the end of the study.

Table II.2. *B. Burgdorferi* assessment and analysis; Serology Test Results

Study Day	Positive for *B. burgdorferi* (Control)	Positive for *B. burgdorferi* (NexGard®)	P-value
-4 (Pre-Treatment)	0/10	0/10	--[1]
27 (Pre-Infestation)	0/10	0/10	--[1]
48	6/10	0/10	--[1]
62	10/10	0/10	--[1]
76	10/10	0/10	--[1]
90	10/10	0/10	--[1]
102	10/10	0/10	--[1]
Overall *B. burgdorferi* infection	10/10	0/10	<0.0001

[1]Fisher's exact test is only computed on the overall *B. burgdorferi* infection defined by both serology tests and PCR test across all time points.

On Day 33, at five days after successful tick infestations (≥ 25% of infesting ticks remained on untreated animal), NexGard® was 99.5% effective against infestations with wild-caught *Ixodes scapularis* ticks ($p < 0.0001$, Table II.3).

Table II.3. Least Squares Mean Live Tick Counts and Percent Effectiveness of NexGard® against wild-caught *I. scapularis* Infestations of Dogs, 5 days after Day 28 Infestations

Days After Treatment	Least Squares Mean Tick Count (Control)	Least Squares Mean Tick Count (NexGard®)	Percent Effectiveness	P-value
33	22.2	0.1	99.5	<0.0001

Adverse Reactions: There were no adverse reactions to NexGard® treatment.

Conclusions: The results of the Lyme Quant C6, SNAP® 4Dx®, and PCR of skin biopsies demonstrated that a single treatment with NexGard® administered 28 days prior to tick infestations prevented *B. burgdorferi* infection by killing *I. scapularis* ticks on the dogs before they could transmit the infection.

2. Laboratory Effectiveness Study

Title: A Study to Evaluate the Ability of a Single Treatment with NexGard® to Reduce the Transmission of *Borrelia burgdorferi* to Dogs from Infected *Ixodes scapularis;* Study PR&D 0328901.

Study Dates: November 12, 2014, to February 12, 2015

Study Location: Athens, GA

Study Design:

Study Objective: To evaluate the ability of a single treatment with NexGard® to prevent the transmission of *Borrelia burgdorferi* to dogs by killing *Ixodes scapularis* vector ticks following an induced infestation with wild-caught, naturally infected *I. scapularis*. This study was conducted in accordance with Good Clinical Practices.

Study Animals: 20 Beagle dogs (10 males, 10 females), 8.5-9.0 months of age, weighing between 9.02-11.42 kg.

Experimental Design: This was a masked study using a randomized block design.

Table II.4. Treatment Groups for Study PR&D 0328901

Treatment Group	Treatment (Minimum Dose)	Treatment Day	Number and Sex of Dogs
1	Control (untreated)	Day 0	10 (5 male, 5 female)
2	NexGard® (2.5 mg/kg)	Day 0	10 (5 male, 5 female)

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.

Measurements and Observations: The primary variables for effectiveness were live tick counts and infection with *B. burgdorferi* defined by serology tests. The Lyme Quant C6® and SNAP® 4Dx® tests (IDEXX laboratories) were used to detect *B. burgdorferi* C6 antibody in order to determine the infection status of each dog throughout the study, from before treatment and tick infestations (Days -6 and 27, respectively) until Days 63, 77 and 92. On Day 28, each dog was infested with 50±5 adult, unfed, wild-caught *I. scapularis* ticks. The ticks had a *B. burgdorferi* infection rate of 67%. The ticks were left on dogs for five days to provide time for feeding and transmission of *B. burgdorferi*. The ticks were removed by combing and counted on Day 33. General health observations were conducted at least once daily for all dogs.

Statistical Methods:

Serology: A dog was determined to be infected with *B. burgdorferi* if a positive result was obtained on either the SNAP® 4Dx® test or the Lyme Quant C6® tests (titer ≥ 30 U/mL) at any sampling time point. For a dog to be considered negative for *B. burgdorferi* infection, a negative result must be obtained for both tests at all sampling time points. The proportion of animals positive for *B. burgdorferi* in the NexGard® group was compared to the proportion of positive

animals in the control group at each sampling time point using Fisher's Exact test.

Tick counts: The percent effectiveness of the NexGard®-treated group with respect to that of the control group was calculated using the formula [(C-T)/C] x 100, where C and T are the Least Squares means estimated from the statistical model on the dogs in the control and NexGard®-treated groups, respectively. The raw tick counts were analyzed using a mixed model analysis of variance with treatment group, sex, and treatment by sex interaction as fixed effects and the allocation blocks as a random effect.

Results: All dogs were seronegative for *B. burgdorferi* before treatment and tick infestations (on Days -6 and 27, respectively). All 10 of the dogs treated with NexGard® remained seronegative for C6 antibody to *B. burgdorferi* by both tests throughout the study, while the proportion of control dogs that became positive increased from Day 48 to 92. On Day 92, 9 of the 10 control dogs were positive for C6 antibody to *B. burgdorferi* in both tests.

Table II.5. *B. burgdorferi* Assessment and Analysis; Serology Test Results

Study Day	Positive for *B. burgdorferi* (Control)	Positive for *B. burgdorferi* (NexGard®)	P-Value
-6 (Pre-Treatment)	0/10	0/10	--[1]
27 (Pre-Infestation)	0/10	0/10	--[1]
48	4/10	0/10	--[1]
63	6/10	0/10	--[1]
77	8/10	0/10	--[1]
92	9/10	0/10	--[1]
Overall *B. burgdorferi* infection	9/10	0/10	0.0001

[1] Fisher's exact test is only computed on the overall *B. burgdorferi* infection defined by both serology tests across all time points.

On Day 33, at five days after successful tick infestations (≥25% of infesting ticks remained alive on untreated animal), NexGard® was 100% effective against infestations with wild-caught *I. scapularis* ticks ($p < 0.001$, Table II.6).

Table II.6. Arithmetic Mean Live Tick Counts and Percent Effectiveness of NexGard® against wild-caught *Ixodes scapularis* Infestations of Dogs, 5 days after Day 28 Infestations

Days After Treatment	Mean Tick Count (Control)	Mean Tick Count (NexGard®)	Percent Effectiveness	P Value
33[1]	21.4	0.0	100.0	<0.001

[1] Counts performed on Day 33, five days after infestations.

Adverse Reactions: There were no adverse reactions to NexGard® treatment.

Conclusions: The results of the Lyme Quant C6® and SNAP® 4Dx® tests demonstrated that a single treatment with NexGard® administered 28 days prior to tick infestations prevented *B. burgdorferi* infection by killing *I. scapularis* ticks on the dogs before they could transmit the infection.

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 141-460, dated September 13, 2013, contains a summary of target animal safety studies for use of NexGard® chewable tablets in dogs at an oral, once-a-month dose of 1.14 mg/lb (2.5 mg/kg).

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that NexGard®, when used according to the label, is safe and effective for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written 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 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 prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

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.