

Date of Approval: April 23, 2025

FREEDOM OF INFORMATION SUMMARY (FOI)
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-554

NexGard® PLUS

(afoxolaner, moxidectin, and pyrantel chewable tablets)

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:

Boehringer Ingelheim Animal Health USA, Inc.

Executive Summary

NexGard® PLUS (afoxolaner, moxidectin, and pyrantel chewable tablets) is approved for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

B. burgdorferi are spirochete bacteria that can cause Lyme disease in dogs. The bacteria are transmitted to a dog through the bite of infected *I. scapularis* ticks, also called black-legged ticks. NexGard® PLUS was previously shown to be effective against these ticks for one month in dogs. The studies that support this supplemental approval showed that the drug kills *I. scapularis* ticks on treated dogs before they can transmit *B. burgdorferi*.

NexGard® PLUS is already approved to prevent heartworm disease caused by *Dirofilaria immitis*; and treat and control adult hookworm (*Ancylostoma caninum*, *Ancylostoma braziliense*, and *Uncinaria stenocephala*) and roundworm (*Toxocara canis* and *Toxascaris leonina*) infections. NexGard® PLUS is approved to kill adult fleas and treat and prevent flea infestations (*Ctenocephalides felis*); and treat and control *I. scapularis*, *Rhipicephalus sanguineus* (brown dog tick), *Dermacentor variabilis* (American dog tick), *Amblyomma americanum* (lone star tick), and *Haemaphysalis longicornis* (longhorned tick) infestations for one month in dogs and puppies eight weeks of age and older, weighing four pounds of body weight or greater.

NexGard® PLUS is an antiparasitic drug with three active ingredients. The drug is available in five strengths of flavored, soft, chewable tablets that are given orally once a month to dogs.

Safety and Effectiveness

The sponsor conducted two laboratory studies in young, healthy, intact male and female beagles. In both studies, on Day 0, the dogs were either administered NexGard® PLUS or sham-dosed (same dosing procedures as the treatment group, but no tablets were administered). On Day 28, the dogs were infested with approximately 50 unfed, wild-caught, adult *I. scapularis* ticks that had a *B. burgdorferi* infection rate of 38.5 to 60%. Live ticks were counted and removed on Day 33.

Blood samples were collected from all dogs on multiple days throughout the study, from 7 to 4 days before treatment to 103 days after treatment. The samples were both qualitatively and quantitatively tested for *B. burgdorferi* antibodies. Skin biopsies from each dog were collected on Day 104 from the heaviest areas of tick attachment, as marked on Day 33, and were quantitatively tested for *B. burgdorferi* by polymerase chain reaction (PCR) testing.

In both studies, NexGard® PLUS was 100% effective at killing *I. scapularis* ticks for 33 days in dogs in the treated group, while dogs in the control group remained infested with live ticks. NexGard® PLUS was also 100% effective at preventing *B. burgdorferi* infections as a direct result of killing *I. scapularis* ticks. In both studies, all dogs treated with NexGard® PLUS remained seronegative for *B. burgdorferi* throughout the study and the bacteria were not detected by PCR testing of the skin biopsies. In contrast, all dogs in the control group in both studies became seropositive for *B. burgdorferi* and the bacteria were detected by PCR testing of the skin biopsies. Diarrhea was reported in

one treated dog in one study. There were no treatment-related adverse reactions in the other study.

The FOI Summary for the original approval of NexGard® PLUS under the same NADA number (NADA 141-554), dated July 19, 2023, contains a summary of target animal safety studies for dogs.

Conclusions

Based on the data submitted by the sponsor for the approval of NexGard® PLUS, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-554

B. Sponsor

Boehringer Ingelheim Animal Health USA, Inc.
3239 Satellite Blvd.
Duluth, GA 30096

Drug Labeler Code: 000010

C. Proprietary Name

NexGard® PLUS

D. Drug Product Established Name

afoxolaner, moxidectin, and pyrantel chewable tablets

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable contains:

9.375 mg afoxolaner, 45 mcg moxidectin, and 18.75 mg pyrantel*

18.75 mg afoxolaner, 90 mcg moxidectin, and 37.5 mg pyrantel*

37.5 mg afoxolaner, 180 mcg moxidectin, and 75 mg pyrantel*

75 mg afoxolaner, 360 mcg moxidectin, and 150 mg pyrantel*

150 mg afoxolaner, 720 mcg moxidectin, and 300 mg pyrantel*

*As pamoate salt

H. How Supplied

NexGard® PLUS is available in five strengths of beef-flavored soft chewables. Each chewable size is available in color-coded packages of one, three, or six chewables.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

NexGard® PLUS is given orally once a month at the minimum dosage of 1.14 mg/lb (2.5 mg/kg) afoxolaner, 5.45 mcg/lb (12 mcg/kg) moxidectin, and 2.27 mg/lb (5.0

mg/kg) pyrantel (as pamoate salt). For heartworm disease prevention, give once monthly for at least six months after last exposure to mosquitoes.

Dosing Schedule:

Body Weight (lbs.)	Afoxolaner Per Chewable (mg)	Moxidectin Per Chewable (mcg)	Pyrantel* Per Chewable (mg)	Chewables Administered
4.0-8.0	9.375	45	18.75	One
8.1-17.0	18.75	90	37.5	One
17.1-33.0	37.5	180	75	One
33.1-66.0	75	360	150	One
66.1-132.0	150	720	300	One
Over 132.0	Not Applicable	Not Applicable	Not Applicable	Administer the appropriate combination of chewables

*As pamoate salt.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

NexGard® PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of adult hookworm (*Ancylostoma caninum*, *Ancylostoma braziliense*, and *Uncinaria stenocephala*) and roundworm (*Toxocara canis* and *Toxascaris leonina*) infections. NexGard® PLUS kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of *Ixodes scapularis* (black-legged tick), *Rhipicephalus sanguineus* (brown dog tick), *Dermacentor variabilis* (American dog tick), *Amblyomma americanum* (lone star tick), and *Haemaphysalis longicornis* (longhorned tick) infestations for one month in dogs and puppies eight weeks of age and older, weighing four pounds of body weight or greater. NexGard® PLUS 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

The effectiveness of NexGard® PLUS to prevent the transmission of *Borrelia burgdorferi* by killing *Ixodes scapularis* ticks on dogs before they can transmit infection, was demonstrated in two well-controlled laboratory studies described below. The original approval of NADA 141-554 dated July 19, 2023, included data that demonstrated the effectiveness of NexGard® PLUS against *I. scapularis* ticks for 30 days.

A. Dosage Characterization

This supplemental approval does not change the previously approved dose of 1.14 mg/lb (2.5 mg/kg) of afoxolaner, 5.45 mcg/lb (12 mcg/kg) of moxidectin, and 2.27 mg/lb (5.0 mg/kg) of pyrantel, given orally once a month. The FOI Summary for the original approval of NADA 141-554 dated July 19, 2023, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study

Title: Effectiveness of a Single Treatment with Afoxolaner + Moxidectin + Pyrantel Administered Orally in a Chewable Formulation for the Prevention of the Transmission of *Borrelia burgdorferi* to Dogs from Infected *Ixodes scapularis*. (Study No. 2021083)

Study Dates: November 14, 2023 to July 15, 2024

Study Location: Athens, GA

Study Design:

Objective: To evaluate the ability of a single treatment with NexGard® PLUS to prevent the transmission of *Borrelia burgdorferi* to dogs following an induced infestation with naturally infected wild-caught *Ixodes scapularis*.

Study Animals: Twenty (20) beagle dogs (11 males and 9 females), 7.4 to 8.2 months of age and weighing 6.42 to 10.04 kg, were included in the study.

Experimental Design: This study was a masked, negative controlled study with a sham-dosed control group. A completely randomized study design was used, and the study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

The study included two treatment groups of 10 dogs per group. One group was sham-dosed and one group was administered NexGard® PLUS at a dose of 2.5 mg/kg of afoxolaner, 12 mcg/kg of moxidectin, and 5 mg/kg of pyrantel (as pamoate salt). The treatment was administered on Day 0. On Day 28, each dog was infested with approximately 50

unfed, wild-caught, adult *I. scapularis* ticks (approximately equal numbers of males and females). The ticks had a *B. burgdorferi* infection rate of 60%.

Table II.I. Treatment groups for Study 2021083

Treatment	Dosage	Day of Treatment	Number of Dogs	Day of Tick Infestation	Day of Tick Count	Days of Blood Collection	Day of Skin Biopsy Collection
Control (sham-dosed)	Not applicable	0	10	28	33	-7, 27, 49, 63, 77, 91, and 103	104
NexGard® PLUS	2.5 mg/kg afoxolaner + 12 mcg/kg moxidectin + 5 mg/kg pyrantel	0	10	28	33	-7, 27, 49, 63, 77, 91, and 103	104

Drug Administration: NexGard® PLUS was administered orally. Dogs were fed prior to treatment. Control dogs did not receive any test article.

Measurements and Observations: Live ticks were counted and removed on Day 33. Blood samples were collected from each dog on Days -7, 27, 49, 63, 77, 91, and 103. Samples were qualitatively tested for *B. burgdorferi* antibodies using the SNAP® 4Dx® Plus Test and quantitatively assayed for *B. burgdorferi* antibodies using Lyme Quant C6® Test. Skin biopsy samples were collected from four sites on each dog on Day 104 from the heaviest areas of tick attachment, as marked on Day 33, and were tested by PCR for the quantitative presence of *B. burgdorferi*. For dogs with fewer than four attachment sites identified, biopsies were collected from the attachment sites identified most frequently on other dogs (neck area). General health observations were conducted at least once daily.

Statistical Methods:

Tick Counts: Percent effectiveness of the NexGard® PLUS-treated group with respect to the control group was calculated for Day 33 using the formula $[(C - T) / C] \times 100$, where C = arithmetic mean calculated from the least squares mean (LSMEAN) of the live tick counts for the control group and T = arithmetic mean calculated from the LSMEAN of the live tick counts for the NexGard® PLUS-treated group. Tick counts were compared using a Fisher-test (F-test). The Mixed Linear Model (MIXED) procedure in SAS version 9.4 was used for the analysis. Treatment group

was listed as a fixed effect and there were no random effects listed. Treatment differences were assessed at the 5% level of significance.

Serology and PCR of Skin Biopsies: A dog was considered to be infected with *B. burgdorferi* if a positive result was obtained on any of the SNAP® 4Dx® Plus Tests for *B. burgdorferi* after Day 28, any of the Lyme Quant C6® Tests after Day 28, and/or any of the four biopsied sites on the Day 104 PCR test.

The proportion of dogs infected with *B. burgdorferi* in the treated group was compared with the proportion of dogs infected in the control group by Fisher's Exact test, which was computed using the frequency (FREQ) procedure in SAS version 9.4. The statistical test was performed at a significance level of 0.05 (two-sided).

Results: Control dogs maintained adequate tick infestations on Day 33, with all 10 controls having at least 12 live ticks. The percent reduction in arithmetic mean live tick counts in the NexGard® PLUS-treated group compared to the control group on Day 33 was 100%. Mean live tick count for the NexGard® PLUS-treated group was significantly lower than for the control group ($p < 0.0001$).

Table II.2. *Ixodes scapularis* Tick Effectiveness: Arithmetic Mean Live Tick Count (Percent Effectiveness)

Day of Tick Count	Control Group Arithmetic Mean Live Tick Count	NexGard® PLUS Arithmetic Mean Live Tick Count	Percent Effectiveness
33	25.1	0.0	100%

All dogs were seronegative for *B. burgdorferi* before treatment and tick infestations, with negative test results on both the SNAP® 4Dx® Plus tests and Lyme Quant C6® tests (titer < 30 U/mL).

Upon completion of the study, all NexGard® PLUS-treated dogs were seronegative for *B. burgdorferi*, with negative test results on both the SNAP® 4Dx® Plus Tests and the Lyme Quant C6® Tests (titer < 30 U/mL), in addition to no detection of *B. burgdorferi* via PCR for all skin biopsies collected on Day 104.

Control dogs were determined to be infected with *B. burgdorferi* at the end of the study, with all 10 control dogs showing positive test results on the SNAP® 4Dx® Plus Test on and after Day 91 and all 10 showing positive results on the Lyme Quant C6® Test (titer ≥ 30 U/mL) on and after Day 63. *B. burgdorferi* infections were detected in all control dogs from at least three of the four skin biopsies collected on Day 103.

Table II.3. SNAP® 4Dx® Plus Results (Serology)

Study Day	Control Dogs Positive	NexGard® PLUS-Treated Dogs Positive
-7	0/10	0/10
27	0/10	0/10
49	4/10	0/10
63	3/10	0/10
77	9/10	0/10
91	10/10	0/10
103	10/10	0/10

Table II.4. Lyme Quant C6® Results (Serology)

Study Day	Control Dogs Positive	NexGard® PLUS-Treated Dogs Positive
-7	0/10	0/10
27	0/10	0/10
49	7/10	0/10
63	10/10	0/10
77	10/10	0/10
91	10/10	0/10
103	10/10	0/10

Table II.5. PCR Test Results (Biopsy)

Study Day	Control Dogs Positive	NexGard® PLUS-Treated Dogs Positive
104	10/10	0/10

Adverse Reactions: There were no treatment-related adverse reactions during the study.

Conclusions: A single oral dose of NexGard® PLUS administered orally to dogs 28 days prior to infestation with *B. burgdorferi*-infected *I. scapularis* ticks prevented *B. burgdorferi* infection as a direct result of killing the *I. scapularis* vector ticks.

2. Laboratory Dose Confirmation Study

Title: Effectiveness of a Single Treatment with Afoxolaner + Moxidectin + Pyrantel Administered Orally in a Chewable Formulation for the Prevention of the Transmission of *Borrelia burgdorferi* to Dogs from Infected *Ixodes scapularis*. (Study No. 2021084)

Study Dates: November 20, 2023 to July 16, 2024

Study Location: Colbert, GA

Study Design:

Objective: To evaluate the ability of a single treatment with NexGard® PLUS to prevent the transmission of *Borrelia burgdorferi* to dogs following an induced infestation with naturally infected wild-caught *Ixodes scapularis*.

Study Animals: Twenty (20) beagle dogs (11 males and 9 females), 7.4 to 8.2 months of age and weighing 8.5 to 11.8 kg, were included in the study.

Experimental Design: This study was a masked, negative controlled study with a sham-dosed control group. A completely randomized study design was used, and the study was conducted in accordance with GCP guidelines.

The study included two treatment groups of 10 dogs per group. One group was sham-dosed and one group was administered NexGard® PLUS at a dose of 2.5 mg/kg of afoxolaner, 12 mcg/kg of moxidectin, and 5 mg/kg of pyrantel (as pamoate salt). The treatment was administered on Day 0. On Day 28, each dog was infested with approximately 50 unfed, wild-caught, adult *I. scapularis* ticks (approximately equal numbers of males and females). The ticks had a *B. burgdorferi* infection rate of 38.5%.

Table II.6. Treatment Groups for Study 2021084

Treatment	Dosage	Day of Treatment	Number of Dogs	Day of Tick Infestation	Day of Tick Count	Days of Blood Collection	Day of Skin Biopsy Collection
Control (sham-dosed)	Not applicable	0	10	28	33	-4, 27, 49, 63, 77, 91, and 103	104
NexGard® PLUS	2.5 mg/kg afoxolaner + 12 mcg/kg moxidectin + 5 mg/kg pyrantel	0	10	28	33	-4, 27, 49, 63, 77, 91, and 103	104

Drug Administration: NexGard® PLUS was administered orally. Dogs were fed prior to treatment. Control dogs did not receive any test article.

Measurements and Observations: Live ticks were counted and removed on Day 33. Blood samples were collected from each dog on Days -4, 27, 49, 63, 77, 91, and 103. Samples were qualitatively tested for *B. burgdorferi* antibodies using the SNAP® 4Dx® Plus Test and quantitatively assayed for *B. burgdorferi* antibodies using Lyme Quant C6® Test. Skin biopsy samples were collected from four sites from each dog on Day 104 from the heaviest areas of tick attachment, as marked on Day 33, and were tested by PCR for the quantitative presence of *B. burgdorferi*. For dogs with fewer than four attachment sites identified, biopsies were collected from the attachment sites identified most frequently on other dogs (neck area). General health observations were conducted at least once daily.

Statistical Methods:

Tick Counts: Percent effectiveness of the NexGard® PLUS-treated group with respect to the control group was calculated for Day 33 using the formula $[(C - T) / C] \times 100$, where C = arithmetic mean calculated from the least squares mean (LSMEAN) of the live tick counts for the control group and T = arithmetic mean calculated from the LSMEAN of the live tick counts for the NexGard® PLUS-treated group. Tick counts were compared using an F-test. The MIXED procedure in SAS version 9.4 was used for the analysis. Treatment group was listed as a fixed effect and

there were no random effects listed. Treatment differences were assessed at the 5% level of significance.

Serology and PCR of Skin Biopsies: A dog was considered to be infected with *B. burgdorferi* if a positive result was obtained on any of the SNAP® 4Dx® Plus Tests for *B. burgdorferi* after Day 28, any of the Lyme Quant C6® Tests after Day 28, and/or any of the four biopsied sites on the Day 104 PCR test.

The proportion of dogs infected with *B. burgdorferi* in the treated group was compared with the proportion of dogs infected in the control group by Fisher's Exact test, which was computed using the FREQ procedure in SAS version 9.4. The statistical test was performed at a significance level of 0.05 (two-sided).

Results: Control dogs maintained adequate tick infestations on Day 33, with all 10 controls having at least 12 live ticks. The percent reduction in arithmetic mean live tick counts in the NexGard® PLUS-treated group compared to the control group on Day 33 was 100%. Mean live tick count for the NexGard® PLUS-treated group was significantly lower than for the control group ($p < 0.0001$).

Table II.7. *Ixodes scapularis* Tick Effectiveness: Arithmetic Mean Live Tick Count (Percent Effectiveness)

Day of Tick Count	Control Group Arithmetic Mean Live Tick Count	NexGard® PLUS Arithmetic Mean Live Tick Count	Percent Effectiveness
33	19.6	0.0	100%

All dogs were seronegative for *B. burgdorferi* before treatment and tick infestations, with negative test results on both the SNAP® 4Dx® Plus tests and Lyme Quant C6® tests (titer < 30 U/mL).

Upon completion of the study, all NexGard® PLUS-treated dogs were seronegative for *B. burgdorferi*, with negative test results on both the SNAP® 4Dx® Plus Tests and the Lyme Quant C6® Tests (titer < 30 U/mL), in addition to no detection of *B. burgdorferi* via PCR for all skin biopsies collected on Day 104.

Control dogs were determined to be infected with *B. burgdorferi* at the end of the study, with all 10 control dogs showing positive test results on the SNAP® 4Dx® Plus Test on and after Day 91 and all 10 showing positive results on the Lyme Quant C6® Test (titer ≥ 30 U/mL) on and after Day 77. *B. burgdorferi* infections were detected in all control dogs from at least three of the four skin biopsies collected on Day 104.

Table II.8. SNAP® 4Dx® Plus Results (Serology)

Study Day	Control Dogs Positive	NexGard® PLUS-Treated Dogs Positive
-4	0/10	0/10
27	0/10	0/10
49	0/10	0/10
63	4/10	0/10
77	9/10	0/10
91	10/10	0/10
103	10/10	0/10

Table II.9. Lyme Quant C6® Results (Serology)

Study Day	Control Dogs Positive	NexGard® PLUS-Treated Dogs Positive
-4	0/10	0/10
27	0/10	0/10
49	9/10	0/10
63	9/10	0/10
77	10/10	0/10
91	10/10	0/10
103	10/10	0/10

Table II.10. PCR Results (Biopsy)

Study Day	Control Dogs Positive	NexGard® PLUS-Treated Dogs Positive
104	10/10	0/10

Adverse Reactions: Diarrhea was reported for one NexGard® PLUS treated dog at the six-hour post-treatment time point.

Conclusions: A single oral dose of NexGard® PLUS administered orally to dogs 28 days prior to infestation with *B. burgdorferi*-infected *I. scapularis* ticks prevented *B. burgdorferi* infection as a direct result of killing the *I. scapularis* vector ticks.

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 141-554 dated July 19, 2023, 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 NexGard® PLUS:

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

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® PLUS, 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 the product is indicated for the prevention of heartworm infections (*Dirofilaria 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.

B. Exclusivity

This supplemental approval for NexGard® PLUS 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 application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indication for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

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 the safety or effectiveness data in the original application.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.