Date of Approval: June 21, 2023

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-406

NexGard®

(afoxolaner)

Chewable Tablet

Dogs

This supplement provides for a new modified NexGard® formulation.

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

This supplement also provides for the addition of label language regarding the improvement of erythema, alopecia, papules, scales, crusts, and excoriation in dogs with flea infestations and signs of Flea Allergy Dermatitis following treatment with NexGard®, as a direct result of eliminating fleas.

Sponsored by:

Boehringer Ingelheim Animal Health USA, Inc.

Executive Summary

NexGard® (afoxolaner) chewable tablets are approved for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. The longhorned tick is a new tick species in the U.S. Not previously found in the Western Hemisphere, these ticks were reported for the first time in the U.S. in 2017.

NexGard® is already approved to 1) kill adult fleas *(Ctenocephalides felis)* and treat and prevent flea infestations; and 2) treat and control *Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), *Amblyomma americanum* (lone star tick), and *Rhipicephalus sanguineus* (brown dog tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. NexGard® is also approved to prevent *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Safety and Effectiveness

The sponsor conducted two laboratory studies to show that NexGard® is effective against *H. longicornis* tick infestations in dogs.

In one study, dogs were experimentally infested with viable, unfed, adult ticks on Day -2 and then weekly for four weeks. On Day 0, dogs in the treatment group were given NexGard® and dogs in the control group were sham-dosed (same dosing procedures as the treatment group, but no tablets were administered). Tick counts were performed on Day 3 (72 hours after treatment) and 72 hours after each weekly infestation. NexGard® was 98.5% effective at controlling *H. longicornis* tick infestations (reducing the number of live ticks) 72 hours after initial infestation and 100% effective 72 hours following all subsequent infestations, while dogs in the control group remained infested with live ticks at each tick count.

In the second study, dogs were experimentally infested with viable, unfed, adult ticks on Day -1 and then weekly for four weeks. On Day 0, dogs in the treatment group were given NexGard® and dogs in the control group were sham-dosed. Tick counts were performed on Day 2 (48 hours after treatment) and 72 hours after each weekly infestation. NexGard® was 100% effective at controlling *H. longicornis* tick infestations (reducing the number of live ticks) throughout the study, while dogs in the control group remained infested with live ticks at each tick count.

In both studies, NexGard® was also effective in treating *H. longicornis* tick infestations. Compared to dogs in the control group, treated dogs had a higher number of dead ticks following all infestations. No adverse reactions were reported in dogs in the treatment group in either study.

The sponsor also conducted a safety and effectiveness field study in dogs living in households naturally infested with fleas to show that NexGard® improves the clinical signs of flea allergy dermatitis (FAD) as a direct result of eliminating fleas. At the first baseline visit between Day -3 and Day 0, all dogs in the household had a physical examination to evaluate overall health as well as for the presence of fleas and signs of FAD: alopecia, erythema, papules, excoriations, or crusts and scales. One dog with at least 10 fleas and 2 signs of FAD was randomly selected as the sentinel dog in each household. All dogs in every enrolled household were treated with either NexGard® or an oral spinosad product for 3 consecutive months.

At each monthly visit on approximately Days 30, 60, and 90, a flea count, an evaluation of signs of FAD, and a physical examination were performed on the sentinel dog only. NexGard® was at least 97.5% effective at controlling flea infestations (reducing the number of live adult fleas) through Day 90. Of the sentinel dogs treated with NexGard®, 70% also showed improvement of the individual signs of FAD at Day 30, which increased to 87.8% at Day 60 and 91.1% at Day 90. There were no serious health abnormalities that were attributed to treatment.

As NexGard® is already approved to kill adult fleas and treat and prevent flea infestations, this study supports the addition of language on the drug's labeling regarding the improvement of signs of FAD following treatment with NexGard®, as a direct result of eliminating fleas. The effectiveness results for controlling flea infestations seen in this study were similar to those reported in the original Freedom of Information (FOI) Summary for the original approval of NADA 141-406 dated September 14, 2013. The FOI Summary for the original approval also contains a summary of target animal safety studies for dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of NexGard®, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-406

B. Sponsor

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

Drug Labeler Code: 000010

C. Proprietary Name

NexGard®

D. Drug 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 1, 3, or 6 beef-flavored chewables.

I. Dispensing Status

Prescription (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 *Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), *Amblyomma americanum* (lone star tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (longhorned tick) 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 a new modified NexGard® formulation.

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

This supplement also provides for the addition of label language regarding the improvement of erythema, alopecia, papules, scales, crusts, and excoriation in dogs with flea infestations and signs of Flea Allergy Dermatitis following treatment with NexGard®, as a direct result of eliminating fleas.

II. EFFECTIVENESS

The effectiveness of NexGard® for the treatment and control of *Haemaphysalis longicornis* infestations was demonstrated in two well-controlled laboratory studies conducted in dogs.

The effectiveness of NexGard® in killing fleas was demonstrated in a 90-day multi-site U.S. field study. In this study, dogs with signs of Flea Allergy Dermatitis (FAD) showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation following treatment, as a direct result of eliminating fleas.

A. Dosage Characterization

This supplemental approval does not change the previously approved 1.14 mg/lb (2.5 mg/kg) dose, administered 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

For the Treatment and Control of Tick Infestations:

1. Laboratory Dose Confirmation Study

   Title: Efficacy of a Single Treatment with NexGard® Administered Orally Against Induced Infestations of Adult *Haemaphysalis longicornis* on Dogs. (Study No. PR&D 0434502)

   Study Dates: June 12, 2020 to June 2, 2021

   Study Location: Bloemfontein, South Africa

   Study Design:

   Objective: To confirm the effectiveness of NexGard® when administered as a single oral dose of at least 2.5 mg/kg, for the treatment and control of induced infestations of adult *H. longicornis* on dogs.

   Study Animals: Twenty (20) dogs (4 male, 16 female), 18.8 to 77.5 months of age and weighing 10.54 to 17.64 kg, were included in the study.

   Experimental Design: The study was conducted in accordance with the Good Clinical Practice (GCP) guidelines. The study included two treatment groups as described in Table II.1. Dogs were infested with approximately 50 adult unfed *H. longicornis* ticks on Days -2, 7, 14, 21, and 28. Live tick counts were performed 72 hours post-treatment or after each infestation. Personnel performing tick counts and health observations were masked to treatment.

Treatment Groups:

Table II.1. Study PR&D 0434502 Treatment Groups

Treatment	Treatment Day	Afoxolaner (mg/kg)	Number of Dogs	Days of Tick Infestations	Days of Live Tick Counts	Days of Dead Tick Counts
NexGard®	0	2.5	10	-2, 7, 14, 21, and 28	3, 10, 17, 24, and 31	1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, 24, 29, 30, and 31
Control (sham-dosed)	0	0	10	-2, 7, 14, 21, and 28	3, 10, 17, 24, and 31	1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, 24, 29, 30, and 31

Drug Administration: Treatments were administered orally once on Day 0. Control dogs did not receive any test article (sham-dosed).

Measurements and Observations: Live and dead ticks were counted on the study days included in Table II.1. Dogs were observed for health abnormalities at 1, 2, 3, and 4 hours after treatment and at least once daily throughout the study.

Statistical Methods: Effectiveness was calculated using the formula 100[(C-T)/C], where C is the arithmetic mean of the live tick counts calculated from the least squares mean of the control group and T is the arithmetic mean of the live tick counts calculated from the least squares mean of the NexGard® treated group at each time point. The least squares mean of each group were obtained from the MIXED procedure in SAS. A mixed model was used to analyze the counts with group listed as a fixed effect. Testing was two-sided at the 5% significance level. The total counts of dead ticks recovered from each dog and from its housing enclosure were used for calculation of arithmetic means by treatment group. For both live and dead ticks, the counts of the NexGard® group were compared to the counts of the control group using an F-test at each time point separately.

Results: NexGard® was 98.5% effective against *H. longicornis* 72 hours following treatment and 100% effective at 72 hours following weekly reinfestations through Day 31. The mean live tick counts of *H. longicornis* for the NexGard®-treated group was less than the mean live tick counts for the control dogs and a statistically significant difference ($p < 0.0001$) was observed on all post-treatment count days. On Days 3 and 10 following treatment administration, a statistically significant difference ($p < 0.0001$ and $p = 0.0230$, respectively), was observed between the mean dead tick counts of *H. longicornis* for the NexGard®-treated group and the mean dead tick counts for the control group. At least 6 dogs in the control group had an

adequate infestation, defined as retention of a minimum of 25% of the original ticks used to infest the animal, at each evaluation time point.

Table II.2. Study PR&D 0434502 Summary of the Live Tick Counts and NexGard® Effectiveness Against *H. longicornis*

Study Day	Control Group Mean Live Tick	NexGard® Group Mean Live Tick	Percent Effectiveness
3	19.5	0.3	98.5%
10	24.4	0.0	100%
17	19.8	0.0	100%
34	20.5	0.0	100%
31	23.1	0.0	100%

Table II.3. Study PR&D 0434502 Summary of the Dead *H. longicornis* Tick Counts

Study Days	Control Group Mean Dead Ticks	NexGard® Group Mean Dead Ticks
1, 2 and 3	1.2	16.9
8, 9 and 10	1.9	6.0
15, 16 and 17	1.2	3.3
22, 23 and 24	1.6	3.3
29, 30 and 31	2.1	3.0

Adverse Reactions: No adverse health events were observed during the study.

Conclusion: NexGard® is effective for the treatment and control of *H. longicornis* on dogs for one month following treatment.

2. Laboratory Dose Confirmation Study

Title: Efficacy of a Single Treatment with NexGard® Administered Orally Against Induced Infestations of Adult *Haemaphysalis longicornis* on Dogs. (Study No. PR&D 0434506)

Study Dates: June 24, 2021 to January 21, 2022

Study Location: Waverly, NY

Study Design:

Objective: To confirm the effectiveness of NexGard® when administered as a single oral dose of at least 2.5 mg/kg, for the treatment and control of induced infestations of adult *H. longicornis* on dogs.

Study Animals: Twenty (20) dogs (6 male, 14 female), 18.8 to 75.8 months of age and weighing 6.1 to 17.5 kg, were included in the study.

Experimental Design: The study was conducted in accordance with the GCP guidelines. The study included two treatment groups as described in Table II.4. Dogs were infested with approximately 50 adult unfed *H. longicornis* ticks on Days -1, 7, 14, 21, and 28. Live tick counts were performed 48 hours post-treatment and 72 hours after each subsequent weekly infestation. Personnel performing tick counts and health observations were masked to treatment.

Treatment Groups:

Table II.4. Study PR&D 0434506 Treatment Groups

Treatment	Treatment Day	Afoxolaner (mg/kg)	Number of Dogs	Days of Tick Infestations	Days of Live Tick Counts	Days of Dead Tick Counts
NexGard®	0	2.5	10	-1, 7, 14, 21, and 28	2, 10, 17, 24, and 31	1, 2, 8, 9, 10, 15, 16, 17, 22, 23, 24, 29, 30, and 31
Control (sham-dosed)	0	0	10	-1, 7, 14, 21, and 28	2, 10, 17, 24, and 31	1, 2, 8, 9, 10, 15, 16, 17, 22, 23, 24, 29, 30, and 31

Drug Administration: Treatments were administered orally once on Day 0. Control dogs did not receive any test article (sham-dosed).

Measurements and Observations: Live and dead ticks were counted on the study days included in Table II.4. Dogs were observed for health abnormalities at 1, 2, 3, and 4 hours after treatment and at least once daily throughout the study.

Statistical Methods: Effectiveness was calculated using the formula 100[(C-T)/C], where C is the arithmetic mean of the live tick counts calculated from the least squares mean of the control group and T is the arithmetic mean of the live tick counts calculated from the least squares mean of the NexGard®-treated group at each time point. The least squares mean of each group were obtained from the MIXED procedure in SAS. A mixed model was used to analyze the counts with group listed as a fixed effect. Testing was two-sided at the 5% significance level. The total counts of dead ticks recovered from each dog and from its housing enclosure were used for calculation of arithmetic means by treatment group. For both live and dead ticks, the counts of the NexGard®-treated group were compared to the counts of the control group using an F-test at each time point separately.

Results: NexGard® was 100% effective against *H. longicornis* 48 hours following treatment and 100% effective at 72 hours following weekly reinfestations through Day 31. The mean live tick counts of *H. longicornis* for

the NexGard®-treated group was less than the mean live tick counts for the control dogs and a statistically significant difference ($p < 0.0001$) was observed on all post-treatment count days. At least 6 dogs in the control group had an adequate infestation, defined as retention of a minimum of 25% of the original ticks used to infest the animal, at each evaluation time point.

Table II.5. Study PR&D 0434506 Summary of the Live Tick Counts and NexGard® Effectiveness Against *H. longicornis*

Study Day	Control Group Mean Live Ticks	NexGard® Group Mean Live Ticks	Percent Effectiveness	P-Value for Live Ticks
2	30.7	0.0	100.0%	< 0.0001
10	21.8	0.0	100.0%	< 0.0001
17	17.0	0.0	100.0%	< 0.0001
24	17.4	0.0	100.0%	< 0.0001
31	18.0	0.0	100.0%	< 0.0001

Table II.6. Study PR&D 0434506 Summary of the Dead *H. longicornis* Tick Counts

Study Days	Control Group Mean Dead Ticks	NexGard® Group Mean Dead Ticks
1 and 2	0.7	26.6
8, 9 and 10	4.2	26.6
15, 16 and 17	2.5	15.6
22, 23 and 24	5.6	10.6
29, 30 and 31	2.2	10.6

Adverse Reactions: No adverse health events were observed during the study.

Conclusions: NexGard® is effective in the treatment and control of *H. longicornis* on dogs for one month following treatment.

Flea Efficacy and Improvement of Signs of Flea Allergy Dermatitis:

3. Field Safety and Effectiveness Study

Title: Effectiveness of NexGard® against Flea Infestations and on Signs of Flea Allergy Dermatitis (FAD) when Administered for Three Consecutive Months to Dogs Naturally Infested with Fleas (*Ctenocephalides felis*). (Study No. PR&D 03547)

Study Dates: February 2017 to February 2018

Study Locations:

San Bernardino, CA
Plaquemine, LA
Bartlesville, OK
West Palm Beach, FL
Antioch, TN
Springfield, MO

Study Design:

Objective: To determine the safety and effectiveness of NexGard® against fleas when administered for three consecutive months to dogs naturally infested with fleas in field settings and evaluate the effect of treatment on signs of flea allergy dermatitis (FAD).

Study Animals: One hundred and three (103) households were enrolled in the study. The households contained a total of 178 dogs which were comprised of a multitude of breeds, mixed and purebred. The dogs were 8 weeks to 14 years old and weighed 4.2 to 124.6 lbs. The enrolled dogs consisted of 52 neutered males, 32 intact males, 61 spayed females, and 33 intact females. One hundred twenty-one (121) dogs treated with NexGard® and 36 dogs treated with oral spinosad completed all four visits of the study.

Experimental Design: This study was an active-controlled, masked, clinical safety and effectiveness study using randomized block design based on order of enrollment of households, where households were assigned to treatment group in a 3:1 ratio of NexGard® to active control. All enrolled households had at least one dog (sentinel) naturally infested with at least 10 fleas and had at least 2 of the following clinical signs associated with flea allergy dermatitis (FAD): alopecia, erythema, papules, excoriations, or crusts and scales. At Visit 1 (the baseline visit, Day -3 to 0), all dogs in the household had a physical examination to evaluate health and confirm the presence fleas and signs of FAD. One dog with at least 10 fleas and signs of FAD was randomly selected from the eligible dogs in each household as the sentinel dog. At Visits 2, 3, and 4 (approximately on Days 30, 60, and 90), flea counts, evaluation of signs of FAD, and physical examinations were performed on the sentinel dog only. The experimental unit for the study was the sentinel dog.

Treatment Groups:

- Group 1: NexGard®
- Group 2: Active control (spinosad)

Drug Administration: NexGard® and active control treatments were administered orally three times at monthly intervals per label directions.

Measurements and Observations: For the flea effectiveness evaluation, live fleas were counted from the sentinel dog from each household on Visits 1, 2, 3, and 4. Clinical signs of FAD (alopecia, erythema, papules, excoriation, and scales/crusts) were observed on the sentinel dog on Visit

1, and the dogs were re-evaluated for these signs on Visits 2, 3, and 4. Physical examinations and abnormalities reported throughout the study for all enrolled dogs were used for evaluation of safety. Personnel performing flea counts and health observations were masked to treatment.

Statistical Methods:

For flea counts, the log-counts from each treatment group were analyzed separately at each post-treatment clinic visit using a repeated measures general linear mixed model. Visit was the fixed effect, and Site, and Site-by-Visit were the random effects. Visit was the repeated measure with the subject defined as dog-within-site. The pivotal analysis compared the counts of Day 30, Day 60, and Day 90 visit with baseline for the treated groups.

NexGard® was considered effective against fleas based on the criteria that the percent effectiveness for fleas at Visit 2 (~Day 30), Visit 3 (~Day 60), and Visit 4 (~Day 90) compared to baseline was ≥ 90% and the Day 30, Day 60, and Day 90 flea counts were statistically significantly different from baseline at the two-sided 0.05 significance level.

Percent Effectiveness = 100 x [(C-T)/C] where C = Geometric mean of the baseline (Day 0) flea counts (anti-logarithm of the least square means minus 1 from the analysis above) and T = Geometric mean of flea counts on the post-treatment visit day (anti-logarithm of the least square means minus 1). This calculation was performed for each post-treatment Visit separately.

For improvement of FAD, the individual skin lesion category scores at Visits 2, 3, and 4 were compared to Visit 1. For each clinical sign related to FAD, NexGard® was considered effective if the proportion of dogs that improved was more than the proportion of dogs that stayed the same or worsened. Changes in the severity of clinical signs were summarized and the percent of dogs showing improvement for each sign was calculated.

Adverse reactions that occurred during the study were summarized and the frequency of occurrence was tabulated.

Results: Sixty-three NexGard®-treated dogs and 20 active control dogs were included in the flea effectiveness analysis on Visit 2. Sixty-three and 59 NexGard®-treated dogs, and 18 and 20 active control dogs, were included in the analysis for Visits 3 and 4, respectively. NexGard® was ≥ 97.5% effective at each of the three flea effectiveness evaluations in this study through Day 90.

Table II.7. PR&D 03547 Percent Effectiveness against live adult *C. felis*

Treatment Group	Study Day (Visit)	Number of Dogs	Baseline Geometric Mean[a]	Visit Geometric Mean[a]	Percent (%) Effectiveness[b]	P-value[c]
NexGard®	Day 30 (Visit 2)	63	24.80	0.62	97.5	< 0.0001
NexGard®	Day 60 (Visit 3)	63	23.20	0.07	99.7	< 0.0001
NexGard®	Day 90 (Visit 4)	59	23.60	0.01	99.9	< 0.0001
Active control	Day 30 (Visit 2)	20	20.92	1.42	93.2	0.0014
Active control	Day 60 (Visit 3)	18	19.69	0.41	97.9	< 0.0001
Active control	Day 90 (Visit 4)	20	20.67	0.14	99.3	< 0.0001

[a] Geometric mean, which was computed by taking the anti-logarithm of the least square mean minus 1.

[b] Percent Effectiveness = 100 x [(C-T)/C], where T and C are the geometric means of the indicated visit and the Day 0 Visit, respectively.

[c] Two-sided probability value was associated with comparing the population flea count means of the Day 0 and indicated visit.

Sixty-one NexGard®-treated dogs were evaluated for improvement in the clinical signs of FAD at Visits 2 and 3, and 57 dogs were evaluated at Visit 4. Eighteen active control dogs were evaluated for improvement of clinical signs of FAD at Visit 2, 15 dogs at Visit 3, and 18 dogs at Visit 4. Of the NexGard®-treated dogs, 70% showed improvement of the individual signs of FAD at Day 30, which increased to 87.8% at Day 60 and 91.1% at Day 90. Of the active control dogs, 53.3% showed improvement of the individual signs of FAD at Day 30, which increased to 81.8% at Day 60 and 81.3% on Day 90.

Table II.8. Number and Percent Improvement from Baseline in Clinical Signs of Flea Allergy Dermatitis by Study Day (Visit).

Study Day (Visit)	FAD Sign	NexGard® Number Improved[a]	NexGard® Percent (%) Improved[a]	Active control Number Improved[a]	Active control Percent (%) Improved[a]
Day 30 (Visit 2)	Alopecia	49 of 58	84.5	8 of 15	53.3
Day 30 (Visit 2)	Erythema	49 of 55	89.1	9 of 15	60.0
Day 30 (Visit 2)	Excoriation	49 of 54	90.7	10 of 15	66.7
Day 30 (Visit 2)	Papules	29 of 37	78.4	8 of 11	72.7
Day 30 (Visit 2)	Scales/Crusts	35 of 50	70.0	11 of 14	78.6
Day 60 (Visit 3)	Alopecia	55 of 59	93.2	9 of 11	81.8
Day 60 (Visit 3)	Erythema	50 of 54	92.6	12 of 13	92.3
Day 60 (Visit 3)	Excoriation	51 of 53	96.2	11 of 11	100.0
Day 60 (Visit 3)	Papules	35 of 36	97.2	8 of 9	88.9
Day 60 (Visit 3)	Scales/Crusts	43 of 49	87.8	12 of 13	92.3
Day 90 (Visit 4)	Alopecia	53 of 55	96.4	12 of 14	85.7
Day 90 (Visit 4)	Erythema	47 of 50	94.0	13 of 16	81.3
Day 90 (Visit 4)	Excoriation	49 of 50	98.0	12 of 13	92.3
Day 90 (Visit 4)	Papules	32 of 33	97.0	10 of 10	100.0
Day 90 (Visit 4)	Scales/Crusts	41 of 45	91.1	14 of 15	93.3

[a] For each clinical sign, the change in FAD score from Baseline for each included dog was calculated as: post-treatment Visit score (if available) minus Day 0 Visit score; if the difference was less than 0, it was categorized as improved; otherwise, it was categorized as having stayed the same or worsened.

Adverse Reactions: Health abnormalities that may have been related to treatment were mild, infrequent, and self-limiting and included emesis, diarrhea, anorexia, pruritis, and lethargy. There were no serious health abnormalities that were attributed to treatment.

Table II.9. Adverse Reactions in Study PR&D 03547

Adverse Reactions	NexGard® N[a]	NexGard® % (n = 130)	Active control N[b]	Active control % (n = 46)
Pruritus	6	4.6	2	4.3
Diarrhea (with and without blood)	5	3.8	1	2.2
Emesis	4	3.1	2	4.3
Anorexia	1	0.8	0	0.0
Lethargy	1	0.8	2	4.3
Seizure	0	0.0	1	2.2

[a] Number of dogs treated with NexGard® with the identified abnormality.

[b] Number of dogs treated with active control with the identified abnormality.

Conclusion: The results of this study demonstrate that NexGard® is effective in the treatment and prevention of flea infestations, when used in various breeds, ages, and weights of dogs under field conditions. Additionally, the dogs treated with NexGard® showed improvement in clinical signs of flea allergy dermatitis over the course of the study as a direct result of eliminating fleas.

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 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 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 treatment and control of *Haemaphysalis longicornis* (longhorned tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. Further, NexGard® has demonstrated an

improvement of erythema, alopecia, papules, scales, crusts, and excoriation in dogs with flea infestations and signs of Flea Allergy Dermatitis following treatment with NexGard®, as a direct result of eliminating fleas.

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 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 indication for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month and the label language regarding the improvement of erythema, alopecia, papules, scales, crusts, and excoriation in dogs with flea infestations and signs of Flea Allergy Dermatitis following treatment with NexGard®, as a direct result of eliminating fleas.

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 Green Book Reports in the Animal Drugs @ FDA database.