Date of Approval: April 1, 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 add language to the Effectiveness section of the package insert from the flea speed of kill study.

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 for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of American Dog tick (*Dermacentor variabilis*) 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 add language to the Effectiveness section of the package insert for the flea speed of kill study.

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. Speed of Kill against Flea Infestations:

a. Laboratory Dose Confirmation Study PR&D 0233403

Title: Speed of Kill of ML-3,663,925 against Induced Infestations of Adult Fleas (*Ctenocephalides felis*) on Dogs Following a Single Oral Dose, Administered to Achieve at Least 2.5 mg/kg

(1) Location:

Merial Limited
Fulton, MO

(2) Study Design:

(a) Objective:

Determine the speed of kill of a single oral dose (at least 2.5 mg/kg) of afoxolaner against induced adult *C. felis* infestations on dogs.

(b) Study Animals:

48 Beagle dogs (24 males, 24 females), 13.8 – 37.5 months of age, weighing between 7.1 – 14.8 kg.

(c) Treatment Groups:

Table 1: Treatment groups for Study PR&D 0233403.

Treatment Group	Dose	Treatment	Frequency/ Duration	Number and Gender of Dogs
1	0 mg/kg	Control (untreated)	Once on Study Day 0	24 (10 M, 14 F)
2	2.5 mg/kg	NEXGARD	Once on Study Day 0	24 (14 M, 10 F)

(d) Drug Administration:

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

(e) Measurements and Observations:

Physical examinations were conducted on Day -12. On Day -1 each dog was infested with 100 ±5 unfed adult fleas (C. felis). Live fleas were removed and counted at 30 minutes, 2, 4, 8, and 12 hours (+/- 30 minutes) post-treatment (4 dogs/treatment group/ timepoint). 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 flea counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula $[(C - T)/C]x100$, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. 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 listed as random effects.

(3) Results:

The percent effectiveness was ≥15.0% against *C. felis* at 2, 4, 8, 12, and 24 hours post-treatment; afoxolaner had no effect (0.0%) at 30 minutes post-treatment (Table 2). Flea counts in the treated group were significantly different ($P < 0.005$) from the control group at the 8, 12, and 24 hour time points, but were not significantly different ($P \geq 0.064$) at 30 minutes, 2, and 4 hours post-treatment.

Table 2: Geometric mean of adult flea counts and percent effectiveness of NEXGARD against induced *C. felis* infestations of dogs.

Time After Treatment	Control Group Geometric Mean	NEXGARD Group Geometric Mean	Percent Effectiveness
30 mins.	62.6	72.7	0.0
2 hours	79.2	67.4	15.0
4 hours	74.3	9.0	87.8
8 hours	65.3	0.3	99.5
12 hours	67.2	0.0	100.0
24 hours	64.5	0.0	100.0

(4) Adverse Reactions:

There were no adverse reactions during this study.

(5) Conclusions:

NEXGARD started to kill fleas 4 hours after initial administration and demonstrated >99% effectiveness at 8 hours.

2. Prevention of Flea Infestations:

a. Overall conclusions on the prevention of flea infestations indication

In the laboratory dose confirmation study (PR&D Study 0232901; see FOI Summary for NADA 141-406 dated September 14, 2013), all dogs were infested with fleas on Day 0, 24 hours prior to treatment with NEXGARD. During this time, the fleas had the ability to initiate feeding, begin mating and start laying eggs, which was confirmed as dogs in both the treated and control groups generated eggs (0-11 eggs and 1-17 eggs at 12- and 24-hours, and 4-90 eggs and 0-118 eggs at 12- and 24-hours post-treatment, respectively). At subsequent evaluations, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 egg), while fleas from dogs in the control group continued to produce eggs (1-141 eggs). Therefore, any adult fleas that hatched from the eggs generated immediately post-treatment and infested a treated dog would be killed, thus inhibiting the perpetuation of the flea infestation. Because female fleas initiate egg laying 24 to 36 hours after their initial blood meal

(Dryden, 1989[1]), the results from the laboratory speed of kill study (PR&D Study 0233403) further support the assertion that any subsequent generations of adult fleas that infested a treated dog would be killed before they are able to lay eggs, thus inhibiting the perpetuation of the flea infestation.

Additionally, the field study supporting substantial evidence of effectiveness for the flea indication (PR&D Study 02341; see FOI Summary for NADA 141-406 dated September 14, 2013) was conducted in households with existing flea infestations of varying severity. After NEXGARD was administered, and the initial flea kill (treatment indication) occurred, dogs were likely re-infested with adult fleas generated from the pre-adult stages already present in the environment. At that point, the study evaluated the perpetuation of flea infestations (prevention indication). Because the field study demonstrated continued effectiveness of NEXGARD against fleas, this study confirmed that NEXGARD inhibited flea infestations on dogs.

Collectively, data from the laboratory speed of kill study (PR&D Study 0233403), laboratory dose confirmation (Study PR&D 0232901), and field effectiveness study (PR&D Study PR&D 02341) support a 30-day effectiveness of a single monthly dose of NEXGARD for the prevention of flea (*C. felis*) infestations on dogs.

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 killing adult fleas and for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of American Dog tick

[1] Dryden, M.W. 1989. Biology of the cat flea, *Ctenocephalides felis felis*. Companion Anim. Prac. 19:23-27

(*Dermacentor variabilis*) 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 an effectiveness study. This exclusivity begins as of the date of our approval letter and only applies to the additional statements in the package insert regarding the flea speed of kill study.

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)(1)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.