Date of Approval: December 19, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-629

MilbeGuard™

(milbemycin oxime)

Flavored Tablets

Dogs and cats

For use in the prevention of heartworm disease caused by *Dirofilaria immitis*, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworms) and *Trichuris vulpis* (whipworm) infections in dogs and in puppies four weeks of age or greater and two pounds body weight or greater.

For use in the prevention of heartworm disease caused by *Dirofilaria immitis*, and the removal of adult *Ancylostoma tubaeforme* (hookworm) and *Toxocara cati* (roundworm) in cats and kittens six weeks of age or greater and 1.5 lbs. body weight or greater.

Sponsored by:

Ceva Sante Animale

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-629

B. Sponsor

Ceva Sante Animale
10 Avenue de la Ballastière
33500 Libourne, France

Drug Labeler Code: 013744

US Agent Name and Address:
Alicia Henk
Ceva Animal Health, LLC
8735 Rosehill Road
Lenexa, KS 66215

C. Proprietary Name

MilbeGuard™

D. Drug Product Established Name

milbemycin oxime

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Flavored tablets

G. Amount of Active Ingredient

2.3 mg, 5.75 mg, 11.5 mg, or 23.0 mg milbemycin oxime per tablet

H. How Supplied

Each tablet size is available in color-coded packages of 6 tablets each, which are packaged 6 per display carton.

I. Dispensing Status

Rx

J. Dosage Regimen

Dogs: MilbeGuard™ Flavored Tablets are given orally, once a month, at the recommended minimum dosage rate of 0.23 mg milbemycin oxime per pound of body weight (0.5 mg/kg).

Table I.1. Recommended Dosage Schedule for Dogs

Body Weight	MilbeGuard™ Flavored Tablets
2-10 lbs.	One tablet (2.3 mg)
11-25 lbs.	One tablet (5.75 mg)
26-50 lbs.	One tablet (11.5 mg)
51-100 lbs.	One tablet (23.0 mg)

Dogs over 100 lbs. are provided the appropriate combination of tablets.

Cats: MilbeGuard™ Flavored Tablets are given orally, once a month, at the recommended minimum dosage rate of 0.9 mg milbemycin oxime per pound of body weight (2.0 mg/kg).

Table I.2. Recommended Dosage Schedule for Cats

Body Weight	MilbeGuard™ Flavored Tablets
1.5-6 lbs.	One tablet (5.75 mg)
6.1-12 lbs.	One tablet (11.5 mg)
12.1-25 lbs.	One tablet (23.0 mg)

Cats over 25 lbs. are provided the appropriate combination of tablets.

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indications

MilbeGuard™ Flavored Tablets are indicated for use in the prevention of heartworm disease caused by *Dirofilaria immitis*, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworms) and *Trichuris vulpis* (whipworm) infections in dogs and in puppies four weeks of age or greater and two pounds body weight or greater.

MilbeGuard™ Flavored Tablets are indicated for use in the prevention of heartworm disease caused by *Dirofilaria immitis*, and the removal of adult *Ancylostoma tubaeforme* (hookworm) and *Toxocara cati* (roundworm) in cats and kittens six weeks of age or greater and 1.5 lbs. body weight or greater.

N. Reference Listed New Animal Drug

Interceptor™; milbemycin oxime; NADA 140-915; Elanco US Inc.

II. BIOEQUIVALENCE

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug (RLNAD)). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD (milbemycin oxime) 5.75 mg flavored tablets. The RLNAD is available in 2.3, 5.75, 11.5, and 23.0 mg tablet sizes. One study was conducted using the 5.75 mg tablet in dogs, and one was conducted using the 5.75 mg tablet in cats. The *in vivo* blood level studies were conducted in 24 healthy beagle dogs and 26 healthy purpose-bred cats. Bioequivalence for both the dog and cat studies was demonstrated between the 5.75 mg RLNAD milbemycin oxime flavored tablets and the 5.75 mg generic milbemycin oxime flavored tablet by demonstrating that the confidence limits for the difference between the pivotal parameters C_{MAX} and AUC are contained within the equivalence limits of 80% and 125%. There were no significant adverse events recorded during the study. *In vitro* comparative dissolution studies were conducted against the 5.75 mg generic lot that was used in the *in vivo* studies to meet the criteria for a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the 2.3 mg, 11.5 mg, and 23.0 mg generic milbemycin oxime flavored tablets for both dog and cat studies. A biowaiver from the requirement to perform *in vivo* bioequivalence studies for the generic 2.3 mg, 11.5 mg, and 23.0 mg milbemycin oxime flavored tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Studies

DOGS:

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of milbemycin oxime (5.75 mg) flavored tablets.

Study Title: A two-way single dose bioequivalence pivotal study of oral milbemycin oxime in dogs, study number P12-022, 16901-12.

Study Date: November 16, 2012 to August 5, 2013

Study Locations:
In-life phase: Sugarland, TX United States
Bioanalytical testing: Colorado Springs, CO United States

Study Design:

Objective: The objective of this study was to determine the comparative in vivo blood-level bioequivalence of Ceva Sante Animale's 5.75 mg generic MilbeGuard™ (milbemycin oxime) flavored tablets and the RLNAD 5.75 mg Interceptor™ (milbemycin oxime) flavored tablets in a randomized, two-period, two-treatment, single-dose crossover study in dogs.

Study Animals: 24 healthy beagle dogs, (13 female/11 male) weighing between 9.3-13.7 kg.

Experimental design: A randomized, two-period, two-treatment, single-dose crossover study with a 14 day washout between periods to evaluate the relative bioavailability of a generic 5.75 mg flavored tablet formulation of MilbeGuard™ (milbemycin oxime) compared to an equivalent dose of the RLNAD Interceptor™

(milbemycin oxime) flavored tablets (Elanco US Inc., NADA 140-915) in 24 healthy beagle dogs.

Drug Administration: The beagles were randomly divided into 2 groups of 12. Each group was administered either the generic milbemycin oxime tablet (5.75 mg) or RLNAD tablet (5.75 mg) during each period.

Measurements and Observations: The plasma concentrations of milbemycin oxime (A3 and A4 analytes) were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events. No significant adverse events were recorded.

Statistical Methods: The study was conducted as a randomized, two-period, two-treatment, single-dose crossover design using 24 dogs with a 14 day washout between periods. The statistical model included treatment, sequence, and period as fixed effects, animal as a random effect, and period as a repeated measure.

Primary variables evaluated for each of the milbemycin oxime analytes (A3 and A4) were area under the curve (AUC) from time 0 to the time the first value below the lower limit of quantitation in the depletion phase is observed and the observed maximum concentration (C_{MAX}). The time to maximum concentration (T_{MAX}) was also evaluated. The method for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus reference, based on the natural log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. To demonstrate bioequivalence, the lower confidence bound should be greater than 80.0%, and the upper confidence bound should be less than 125.0% for both AUC and C_{MAX}.

Results: As seen in the tables below, AUC and C_{MAX} fall within the prescribed bounds for both the A3 milbemycin oxime analyte (Table II.1) and the A4 milbemycin oxime analyte (Table II.2). T_{MAX} values obtained for the test product and reference product indicate that these drugs will provide equivalent therapeutic results.

Table II.1. Bioequivalence Evaluation for A3 Analyte in Dogs

Parameter	Test Mean	Reference Mean	Ratio◇	Lower Bound (%)	Upper Bound (%)
AUC (µg/mL)*hour	474.92†	488.22†	0.97	92.85	101.91
C_{MAX} (µg/mL)	37.72†	38.45†	0.98	89.31	107.79
T_{MAX} (hours)	1.43‡	1.46‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
◇ Ratio = Test/Reference
NE = not estimated

Table II.2. Bioequivalence Evaluation for A4 Analyte in Dogs

Parameter	Test Mean	Reference Mean	Ratio◇	Lower Bound (%)	Upper Bound (%)
AUC (µg/mL)*hour	2632.33†	2507.48†	1.05	100.10	110.10
C_{MAX} (µg/mL)	196.72†	187.33†	1.05	97.95	112.58
T_{MAX} (hours)	1.61‡	1.58‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
◇ Ratio = Test/Reference
NE = not estimated

Adverse Reactions: No significant adverse reactions were reported in this study.

Conclusion: Bioequivalence between the 5.75 mg generic MilbeGuard™ (milbemycin oxime) flavored tablets (test) and the RLNAD 5.75 mg Interceptor™ (milbemycin oxime) flavored tablets (reference) has been established in the *in vivo* bioequivalence study.

CATS:

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of milbemycin oxime (5.75 mg) flavored tablets.

Study Title: Pivotal Bioequivalence Study of Piedmont's Milbemycin Oxime Tablets with INTERCEPTOR® (Milbemycin Oxime) Flavor Tabs in Cats, study number P13-007 and KFI-062-BF-1013

Study Date: June 6, 2013 to November 5, 2013

Study Locations:
In-life phase: Stouffville, ON, Canada
Bioanalytical testing: Colorado Springs, CO United States

Study Design:

Objective: The objective of this study was to determine the comparative in vivo blood-level bioequivalence of Ceva Sante Animale's 5.75 mg generic MilbeGuard™ (milbemycin oxime) flavored tablets and the RLNAD 5.75 mg Interceptor™ (milbemycin oxime) flavored tablets in a randomized, four-period, single-dose double crossover study in cats.

Study Animals: 26 healthy, purpose-bred cats (13 male, 13 female). Test animals weighed between 2.3 to 5.8 kilograms.

Drug Administration: Each cat received Test and Reference treatment twice during the study. Each cat was administered one 5.75 mg tablet of test or reference article at a time.

Experimental Design: A randomized, four-period, single-dose double crossover study with 14 day washouts between periods to evaluate the relative bioavailability of a generic 5.75 mg flavored tablet formulation of MilbeGuard™ (milbemycin oxime) compared to an equivalent dose of the RLNAD Interceptor™ (milbemycin oxime) flavored tablets (Elanco US Inc., NADA 140-915) in 26 healthy, purpose-bred cats.

Measurement and Observations: The plasma concentrations of milbemycin oxime (A3 and A4 analytes) were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events. No significant adverse events were recorded.

Statistical Methods: The study was conducted as a randomized, four-period, single-dose double crossover design using 26 cats with 14-day washouts between periods. The statistical model included treatment, sequence, and period as fixed effects and animal within sequence as a random effect.

Primary variables evaluated for each of the milbemycin oxime analytes (A3 and A4) were area under the curve (AUC) from time 0 to the time the first value below the lower limit of quantitation in the depletion phase is observed and the observed maximum concentration (C_{MAX}). The time to maximum concentration (T_{MAX}) was also evaluated. The method for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus reference, based on the natural log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. To demonstrate bioequivalence, the lower confidence bound should be greater than 80.0%, and the upper confidence bound should be less than 125.0% for both AUC and C_{MAX}.

Results: As seen in the tables below, AUC and C_{MAX} fall within the prescribed bounds for both the A3 milbemycin oxime analyte (Table II.3) and the A4 milbemycin oxime analyte (Table II.4). T_{MAX} values obtained for the test product and reference product indicate that these drugs will provide equivalent therapeutic results.

Table II.3. Bioequivalence Evaluation for A3 Analyte in Cats

Parameter	Test Mean	Reference Mean	Ratio◇	Lower Bound (%)	Upper Bound (%)
AUC (ng/mL)*hour	378.12†	381.80†	0.99	86.24	113.74
C_{MAX} (ng/mL)	51.13†	50.86†	1.01	92.59	109.19
T_{MAX} (hours)	2‡	2‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
◇ Ratio = Test/Reference
NE = not estimated

Table II.4. Bioequivalence Evaluation for A4 Analyte in Cats

Parameter	Test Mean	Reference Mean	Ratio◇	Lower Bound (%)	Upper Bound (%)
AUC (ng/mL)*hour	3986.23†	4079.79†	0.98	91.41	104.44
C_{MAX} (ng/mL)	340.22†	358.17†	0.95	88.39	102.09
T_{MAX} (hours)	2‡	2‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
◇ Ratio = Test/Reference
NE = not estimated

Adverse Reactions: No significant adverse reactions were reported in this study.

Conclusion: Bioequivalence between the 5.75 mg generic MilbeGuard™ (milbemycin oxime) flavored tablets (test) and the RLNAD 5.75 mg Interceptor™ (milbemycin oxime) flavored tablets (reference) has been established in the *in vivo* bioequivalence study.

B. Bioequivalence Waiver

Pivotal *in vivo* blood-level bioequivalence studies were conducted using the 5.75 mg milbemycin oxime flavored tablet strength in dogs and cats.

A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 2.3 mg, 11.5 mg, and 23.0 mg milbemycin oxime flavored tablets was requested. To qualify for a biowaiver for each of these product strengths, comparative dissolution studies were conducted to determine the dissolution profiles of the generic 2.3 mg, 5.75 mg, 11.5 mg, and 23.0 mg milbemycin oxime flavored tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 5.75 mg and generic 2.3 mg tablets
- Generic 5.75 mg and generic 11.5 mg tablets
- Generic 5.75 mg and generic 23.0 mg tablets

Dissolution parameters:

- Dissolution apparatus: Apparatus II (paddle)
- Dissolution medium: 0.2% sodium lauryl sulfate (SLS)
- Dissolution medium volume: 900 mL (per vessel)
- Paddle speed: 75 rpm
- Temperature: 37.0 °C ± 0.5 °C
- Number of vessels: 6
- Analytical method: HPLC with UV detection
- Sampling times: 5, 15, 30, 45, 60, and 90 minutes

The biolot used in the *in vivo* bioequivalence studies was the same lot used to support the *in vitro* profile comparisons. Analytical method validation was required

to ensure that the quantification of drug concentrations in all samples was accurate and precise.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 5 minutes) should not be more than 20% and at other time points should not be more than 10%. The percent coefficient of variation for all generic product profiles were within acceptable limits. Only one measurement should be considered after 85% dissolution of both products. The similarity factor (f_2) should be greater than 50 to ensure sameness or equivalence of two profiles.
CVM estimated f_2 metrics based on mean data, and a summary of the results is presented in the following table:

Table II.5. Calculated f_2 values

	Generic 2.3 mg flavored tablet	Generic 11.5 mg flavored tablet	Generic 23.0 mg flavored tablet
Generic 5.75 mg flavored tablet	$f_2 = 63$	$f_2 = 72$	$f_2 = 72$

The study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 2.3 mg, 11.5 mg, and 23.0 mg milbemycin oxime flavored tablets was granted.

III. EFFECTIVENESS

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in dogs and cats, which are not food producing animals.

VI. USER SAFETY

CVM did not require user safety studies for this approval.
The product labeling contains the following information regarding safety to humans handling, administering, or exposed to MilbeGuard™:

Keep this and all drugs out of the reach of children.

VII. AGENCY CONCLUSIONS

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that MilbeGuard™, when used according to the label, is safe and effective.