Freedom of Information Summary

MILBEMITE™ OTIC Solution
NADA 141-163

"for the treatment of ear mite (*Otodectes cynotis*) infestations in cats and kittens eight weeks of age and older. Effectiveness is maintained throughout the life cycle of the ear mite."

Sponsored by:

Novartis Animal Health US, Inc.
Post Office Box 26402
Greensboro, NC 27404-6402

Table of Contents

1. GENERAL INFORMATION:

NADA Number: NADA 141-163

Sponsor: Novartis Animal Health US, Inc.
Post Office Box 26402
Greensboro, NC 27404-6402

Generic Name: Milbemycin Oxime Solution

Trade Name: MILBEMITE™ OTIC Solution

Marketing Status: Rx

II. INDICATIONS FOR USE:

MILBEMITE OTIC Solution is indicated for treatment of ear mite (*Otodectes cyanotis)* infestations in cats and kittens eight weeks of age and older. Effectiveness is maintained throughout the life cycle of the ear mite.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND DOSAGE:

MILBEMITE OTIC Solution is a solution containing milbemycin oxime. MILBEMITE OTIC Solution is recommended for use in cats 8 weeks of age and older.

Dosage Form: 0.1% milbemycin oxime solution

Route of Administration: Topical application into the external ear canal

Dosage and Administration: Administer as a single treatment of one ampoule per ear followed by massaging the base of the ear to distribute the drug**.** Cleaning of the external ear canal prior to treatment may be performed, but is not necessary to provide effectiveness.

IV. EFFECTIVENESS:

A. DOSAGE RATIONALE:

The results of two pilot studies demonstrated that concentrations of 0.01% and 0.001% milbemycin oxime solution did not provide adequate effectiveness (≥ 90%) for the treatment of *Otodectes cyanotis* infestations in cats. In the first study, twelve household cats (6 males, 6 females), positive for ear mites, were assigned to a milbemycin (0.01%) or vehicle treatment group. In the second study, two cats positive for ear mites, were assigned to a milbemycin (0.001%) or vehicle treatment group. For both studies, a single treatment (0.2 mL) was administered in both ears on day 0. On day 7, each cat's ears were checked for the presence of ear mites. For the first study on day 7, 5/6 milbemycin-treated and 2/6 vehicle treated cats were negative for ear mites. For the second study on

day 7, none of the cats were negative for ear mites. A concentration of 0.1% was selected for further evaluation.

B. LABORATORY DOSE CONFIRMATION STUDY:

Title: Dose Confirmation Study of Milbemycin Oxime Solution for the Treatment of Ear Mites (*Otodectes cynotis*) On Cats.

Purpose: To confirm the effectiveness of 0.1% milbemycin oxime solution in the treatment of ear mites (*Otodectes cynotis)* in naturally infested cats.

Investigator/Study Location**:** Janice O. Kuhn, PhD, DABT
Stillmeadow, Inc.
12852 Park One Drive
Sugar Land, Texas 77478

Animals: 20 adult cats (7 males, 13 females), 5 months to three years of age, 10 per group

Dosage Groups: 0.2 mL (0.1% milbemycin oxime solution)
0.2 mL (vehicle)

Route of Administration: Topical application into the external ear canal

Frequency of Treatment: Single treatment on Day 0

Duration of Study: 30 days

Study Design: All cats had natural ear mite infestations in either one or both ears prior to enrollment. Each cat's ears were swabbed prior to treatment. The cats received treatment on day 0. Clinical observations were noted hourly for the first four hours and daily through day 30. Ear mite evaluations were conducted on days 7 and 30.

Parameters Measured: Ear mite presence

Results: NUMBER OF CATS WITH EAR MITES AND PERCENT SUCCESS

	NUMBER OF CATS WITH EAR MITES				
TREATMENT GROUP	PRE-TREATMENT	DAY 7	DAY 30	% Success Day 7	% Success Day 30
0.1% milbemycin oxime	10	0	0	100%	100%
vehicle	10	9	8	10%	20%

Percent Success = $\frac{\text{\# Cats positive pre-treatment - \# Cats positive post-treatment}}{\text{\# Cats positive pre-treatment}} \times 100$

Conclusions: The 0.1% milbemycin oxime solution was 100% effective in eradicating ear mite infestations in the test animals after one treatment.

Adverse Reactions: There were no reported adverse reactions attributable to the treatment.

C. CLINICAL FIELD TRIAL

Title: Controlled Clinical Field Trial to Determine Effectiveness of Milbemycin Oxime Solution for the Treatment of Ear Mites **(***Otodectes cynotis)* in Cats

Purpose: To confirm the effectiveness and safety of 0.1% milbemycin oxime solution used in the treatment of ear mite infestations (*Otodectes cynotis)* in naturally infested cats presented to veterinary clinics.

Investigators/Study Locations:

Dr. Jay Butan
Canal Animal Hospital
Lake Worth, FL

Dr. William Campaigne
Seguin Animal Hospital
Seguin, TX

Dr. Joseph Kinnarney
Reidsville Veterinary Hospital
Reidsville, NC

Dr. James Hicks
Arlington Animal Hospital
Riverside, CA

Dr. Edward Jezbera
Riverside Animal Hospital
Riverside, CA

Dr. Lynn Roberts
Pilot Mountain Animal Hospital
Pilot Mountain, NC

Dr. Lynn Roberts
Rural Hall Animal Hospital
Rural Hall, NC

Dr. Leonard Sigdestad
Loma Linda Animal Hospital
San Bernardino, CA

Dr. Johnnie R. Vaughan
Tenn-Tran Animal Clinic and Reproductive Center
Somerville, TN

Animals: A total of 201 cats (100 males and 101 females) ranging in age from 4 weeks to 17 years were enrolled in the study. Milbemycin (0.1%) or placebo solutions were administered in both ears of each cat on day 0. One hundred ninety-seven cats (102 milbemycin and 95 placebo) returned on visit 2 and one hundred twenty nine (96 milbemycin and 33 placebo) on visit 3. Statistical analyses were conducted on these cases.

Dosage Groups: 0.2 mL (0.1% milbemycin oxime solution)
0.2 mL (vehicle)

Route of Administration: Topical application into the external ear canal

Frequency of Treatment: Single treatment on day 0.

Duration of Study: 28-35 days

Parameters Measured: Ear mite presence (days –1, 7-10 and 28-35).

Results: The effectiveness of a single dose of 0.1% milbemycin oxime solution was 99% compared to group B, the placebo group, which demonstrated 17% effectiveness. Many animals still had debris in their ears at the end of the study.

Conclusions: The effectiveness of a single dose of 0.1% milbemycin oxime solution applied aurally is 99% after 7 and 30 days. The number of kittens enrolled less than 8 weeks of age was not adequate to evaluate the safety of the drug in these young animals.

Adverse Reactions: There were no reported adverse reactions attributable to the treatment.

V. TARGET ANIMAL SAFETY:

Title: Target Animal Safety Study of Milbemycin Oxime Solution for the Treatment of Ear Mites (*Otodectes cyanotis*) on Cats

Purpose: To demonstrate the safety of three dosage levels of 0.1% milbemycin oxime solution administered in the ears of 6 month old cats.

Investigator/Study Location: Janice O. Kuhn, PhD, DABT
Stillmeadow, Inc.
12852 Park One Drive
Sugar Land, Texas 77478

Animals: 24 cats (12 males and 12 females), 6 months of age and older, 8 cats per group (4 males and 4 females)

Dosage Groups: Group I 1X (0.1% milbemycin oxime solution)
Group II 3X (0.1% milbemycin oxime solution)
Group III 5X (0.1% milbemycin oxime solution)

Route of Administration: Topical application into the right ear canal only. The left ear remained untreated.

Frequency of Treatment: Treated once weekly for three weeks.

Group I, 1X (0.2 mL, one single dose tube)
Group II, 3X (0.6 mL, three single dose tubes)
Group III, 5X (1.0 mL, five single dose tubes)

Duration of Study: 21 days

Parameters measured: A physical exam was performed prior to study initiation. The cats were examined daily to determine pharmacologic and/or toxicologic drug effects and for dermal irritation in the ears on days 0-21. At study termination, the external ear canals were biopsied and examined histologically for dermal irritation and inflammation. Body weights and food consumption were recorded throughout the study. Blood specimens were collected and analyzed for milbemycin oxime levels throughout the study for Group III (5X).

Results: There were no reported adverse reactions attributable to treatment. No detectable levels of milbemycin were reported in the blood samples collected from the cats in the 5X group.

Conclusions: Otic doses of 0.1% milbemycin oxime administered once weekly for three weeks to 8 healthy adult cats from the 5X group (total of three 1.0 mL doses), did not produce adverse systemic or local effects. Each 1.0 mL dose contained 1.0 mg of milbemycin which represents 2.5X the recommended dose of MILBEMITE OTIC Solution (bilateral treatment). This dose did not result in measurable levels of milbemycin in the blood [assay limit of quantitation (LOQ) of 0.02 ppm] in any of the samples taken over the 3-week treatment period. In consideration of the absence of quantifiable milbemycin oxime blood levels and the relatively small administered doses after otic administration as compared to those tested in oral target animal safety (TAS) studies, systemic safety concerns have been adequately addressed by the oral TAS studies. Refer to Novartis Animal Health's NADA 140-915 Freedom of Information Summary dated April 13, 1998, for a disclosure of the TAS studies conducted for the oral formulation in cats.

VI. HUMAN SAFETY:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in cats which are non-food animals.

Human Warnings are provided on the product label as follows: **"**Not for human use. Keep this and all drugs out of the reach of children."

VII. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that MILBEMITE OTIC Solution, when used under the labeled conditions of use, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian to monitor the safe use of this new product.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non-food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

Novartis holds patent No. 4,547,520 and expires June 14, 2004.

VIII. LABELING (ATTACHED):

A. Veterinarian Insert
B. Foil Pouch
C. Tube Label
D. Unit Dose Carton

VETERINARIAN INSERT

MILBEMITE™ OTIC Solution
(0.1% milbemycin oxime)

Caution:
U.S. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
MILBEMITE OTIC Solution is available in plastic dispensing tubes with break off tips. Each plastic tube contains 0.25 mL of MILBEMITE OTIC Solution as a 0.1% solution of milbemycin oxime. Milbemycin oxime consists of the oxime derivatives of 5-didehydromilbemycins in the ratio of approximately 80% A_4 ($C_{32}H_{45}NO_7$, MW 555.71) and 20% A_3 ($C_{31}H_{43}NO_7$, MW 541.68).

Indications:
MILBEMITE OTIC Solution is indicated for treatment of ear mite (*Otodectes cynotis)* infestations in cats and kittens eight weeks of age and older. Effectiveness is maintained throughout the life cycle of the ear mite.

Human Warnings:
Not for human use. Keep this and all drugs out of the reach of children.

Precautions:
The safe use of MILBEMITE OTIC Solution in kittens less than eight weeks of age and in cats used for breeding purposes, during pregnancy, or in lactating queens, has not been evaluated.

Adverse Reactions: No adverse reactions caused by MILBEMITE OTIC Solution have been reported in controlled safety and effectiveness studies in cats.

Dosage:
MILBEMITE OTIC Solution should be administered topically into the external ear canal as the entire contents of a single dose tube per ear. The volume delivered will be approximately 0.2mL, with 0.05mL residual volume remaining in dispensing tube. Safety of repeated treatments has not been evaluated.

Administration:
MILBEMITE OTIC Solution should be administered as one tube per ear as a single treatment. Each foil pouch contains two tubes of solution, one for each ear. Open the tube by snapping off the cap. Squeeze the tube to administer the contents of one tube into each external ear canal. Massage the base of the ear for optimal distribution. In clinical field trials, ears were not cleaned and many animals still had debris in their ears at the end of the study. Cleaning of the external ear canal prior to treatment may be performed, but is not necessary to provide effectiveness.

Effectiveness:

The clinical effectiveness of milbemycin oxime 0.1% solution was evaluated in a placebo-controlled clinical field trial of client-owned cats. *Otodectes cynotis* infestation was diagnosed by direct microscopic visualization of ear swab debris. Test or placebo treatment was administered to both ears of the cat following the pre-treatment examination. Cats' ears were examined by ear swab microscopy at multiple intervals throughout the life cycle of the mite (up to day 30). Ninety-nine percent (99%) of the milbemycin oxime treated group were ear mite negative at the microscopic exams.

Safety:
A study was conducted to evaluate the safety of a 0.1% milbemycin oxime solution in adult cats. Topical doses at 1x, 3x or 5x the recommended dose applied in one ear did not produce adverse effects. In addition, no measurable levels of the milbemycin were detected in whole blood of the cats dosed at 5x.

Storage Conditions:
MILBEMITE OTIC Solution should be stored at controlled room temperature, between 59° and 86° F (15°-30° C).

How Supplied:
MILBEMITE OTIC Solution is supplied in individual white polypropylene tubes, paired in a foil overlay pouch. The product is packaged in a box of 10 pouches of 2 tubes of 0.25 mL each.

NADA #141-163, Approved by FDA

U.S. Patent No. 4,547,520

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27404 USA

NOVARTIS