FREEDOM OF INFORMATION SUMMARY

ACAREXX™
(0.01% ivermectin) otic suspension

"..for the treatment of adult ear mite (*Otodectes cynotis*) infestations in cats and kittens four weeks of age or older. Effectiveness against eggs and immature stages has not been proven."

Sponsored by:

Blue Ridge Pharmaceuticals, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

Table of Contents

I. GENERAL INFORMATION:

NADA Number: 141-174

Sponsor: Blue Ridge Pharmaceuticals, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

Generic Name: Ivermectin otic suspension

Trade Name: ACAREXX™

Marketing Status: Rx

II. INDICATIONS FOR USE:

ACAREXX is indicated for the treatment of adult ear mite (*Otodectes cynotis*) infestations in cats and kittens four weeks of age or older. Effectiveness against eggs and immature stages has not been proven.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE:

Dosage Form: 0.01% ivermectin otic suspension

Route of Administration: Topical application in ear canal

Dosage and Administration: One dose of 0.5 mL is applied in each ear. Repeat treatment one time if necessary, based upon the ear mite life cycle and the response to treatment.
Tear the foil pouch at the notch to remove the two plastic ampules. Use one ampule per ear. Shake well before use. Snap off the cap of the ampule and place the tip into the external ear canal. Squeeze the entire contents of one ampule into the ear and massage the base of the ear to distribute the medication. Repeat the procedure in the other ear using the second ampule. Cleaning the ears prior to administration of ACAREXX is not necessary to provide effectiveness.

IV. EFFECTIVENESS:

LABORATORY DOSE TITRATION/CONFIRMATION STUDY

1. Title: Dose Titration of Ivermectin Otic Suspension for the Treatment of Ear Mites (*Otodectes cynotis*) in Cats. Study Protocol Number: BRP-LIM-0197

   Purpose: To determine that 0.5 mL of a 0.001%, 0.01% or 0.1% ivermectin otic suspension per ear is effective for the treatment of ear mites (*Otodectes cynotis*) in cats.

   Investigator: Dr. Dwight D. Bowman

   Study Location: Cheri-Hill Kennel R&D
   Stanwood, Michigan 49346

   Animals: 48 cats (29 Males, 19 Females) young to adult, 12 per group.

   Dosage Groupings: A: 0.5 mL Placebo (saline without active ingredient)
   B: 0.5 mL 0.001% ivermectin otic suspension
   C: 0.5 mL 0.01% ivermectin otic suspension
   D: 0.5 mL 0.1% ivermectin otic suspension

   Route of Administration: Topical application into the ear canal.

   Frequency of Treatment: Single treatment on Day 0

   Study Design: All cats had a natural ear mite infestation in either one or both ears. Cat's ears were swabbed prior to treatment (Day –1) to confirm ear mite infestations. The ears were not cleaned prior to treatment or during the study. The cats received treatment on day 0 and the ears were massaged for ten seconds. All animals were observed hourly for the first four hours post-dosing and then daily afterward. Seven days after treatment (Day 7), a repeat swab was performed on the ears to examine for the presence of ear mites.

   Parameters Measured: Ear mite presence.

Results:

	Number Cats Positive/Total Number of Cats		
	Day 0	**Day 7**	**% Improved**
Placebo	12/12	10/12	17
0.001%	12/12	0/12	100
0.01%	12/12	1/12	92
0.1%	12/12	0/12	100

Conclusions: Ivermectin otic suspension was effective at a single dose of 0.001%, 0.01%, or 0.1% in treating adult ear mite infestations in cats for one week. A dose of 0.01% was selected for further studies.

Adverse Reactions: On the day of treatment, one cat vomited food within one hour of receiving 0.5 mL per ear of 0.01% ivermectin otic suspension. Another cat which received 0.5 mL per ear of 0.01% ivermectin otic suspension had painful ears due to inflammation on Day 7 which was not noted on Day -1.

CLINICAL FIELD TRIAL

2. Title: Controlled Clinical Trial of Ivermectin Otic Suspension for the Treatment of Ear Mites (*Otodectes cynotis*) in Cats

   Purpose: To confirm the effectiveness and safety of 0.01% ivermectin otic suspension used in the treatment of ear mite infestations in cats presented as veterinary patients.

   Investigators/Study Locations:

   Dr. William Campaigne
   Seguin Animal Hospital
   1252 West Kingsbury Street
   Seguin, TX 78155

   Dr. Edward Jezbera
   Riverside Animal Hospital
   6162 Magnolia Avenue
   Riverside, CA 92506

   Dr. James Hicks
   Arlington Animal Hospital
   4229 Van Buren Boulevard
   Riverside, CA 92503

   Dr. Joseph Kinnarney
   Reidsville Veterinary Hospital
   1401 W. Harrison Street
   Reidsville, NC 27320

   Dr. Lynn Roberts
   Pilot Mountain Animal Hospital
   605 Key Street - HWY 268
   Pilot Mountain, NC 27041

   Dr. Leonard Sigdestad
   Loma Linda Animal Hospital
   2605 South Waterman Avenue
   San Bernardino, CA 92408

   Dr. Lynn Roberts
   Rural Hall Animal Hospital

   Dr. Jan Strother
   N. Alabama Cat & Bird Veterinary

1055 Highway 65
Rural Hall, NC 27045

Clinic
Route 4, Box 92
Hartselle, AL 35640

Dr. Roger Sifferman
Bradford Park Veterinary Hospital
1255 E. Independence
Springfield, MO 65804

Animals: A total of 160 cats were enrolled in the study. Of these, 139 client owned cats (79 males and 60 females) ranging in age from 4 weeks to 16 years, were treated with either placebo or 0.01% ivermectin otic suspension and included in the final analysis. Sixty-eight of the 139 cats (35 males and 33 females) ranging in age from 8 weeks to 12 years, were treated with the test material (0.01% ivermectin).

Dosage Groups:
A: 0.5 mL 0.01% ivermectin otic suspension
B: 0.5 mL Placebo (suspension without active ingredient)
C: 0.5 mL Placebo (suspension without active ingredient)
D: 0.5 mL 0.01% ivermectin otic suspension

Route of Administration: Topical application into the ear canal.

Frequency of Treatment: Single treatment

Duration of Study: 7 - 10 days

Parameters Measured: Cat's ears were swabbed to examine for the presence of ear mites prior to treatment and 7-10 days after treatment. Ear mite presence was recorded.

Results: Groups A and D cats that received 0.01% ivermectin otic suspension showed 94% effectiveness compared to groups B and C, the placebo groups, which showed 21% effectiveness. Cats and kittens enrolled in this study received other frequently used veterinary products safely, such as flea control products, vaccines, anthelmintics, antibiotics, and steroids.

Conclusions: The effectiveness of a single dose of 0.01% ivermectin otic suspension applied aurally, in controlling ear mite infestations in cats is 94% after 7-10 days.

Adverse Reactions: No reactions were reported that were related to the test material.

V. ANIMAL SAFETY:

1. Title: Target Animal Safety Study of a Test Article in the Ears of Approximately Four Week Old Kittens, Laboratory Study # 3978-97

   Purpose: To determine the safety and potential dermal irritation of three dosage levels of ivermectin otic suspension in the ears of 4 week old kittens.

   Investigator: Janice O. Kuhn, Ph.D., D.A.B.T.

   Study Location: Stillmeadow, Inc.
   Sugar Land, Texas 77478-2521

   Animals: 24 kittens (13 males and 11 females), approximately 4 weeks old, 6 kittens per group (Group I: 4 males and 2 females, Group II – IV: 3 males and 3 females).

   Dosage Groups: Group I: Untreated control
   Group II: 1X (0.01% ivermectin otic suspension)
   Group III: 3X (0.01% ivermectin otic suspension)
   Group IV: 5X (0.01% ivermectin otic suspension)

   Route of Administration: Topical application into the ear canal.

   Frequency of Treatment: Treated once a day for three consecutive days:
   Group II, 1X Once a day
   Group III, 3X (1X three times)
   Group IV, 5X (1X five times)

   Duration of Study: 10 days

   Parameters measured: A physical exam was performed on day –4. The kittens were observed daily for signs of pharmacologic and/or toxicologic effects and for dermal irritation in the ears. At Day 10, a biopsy of the external ear canal was obtained and examined histologically for dermal irritation or inflammation. Body weights were recorded on days –1 and 10.

   Results: At the 5X dose, four out of six animals in the group had scratches on their ears, and two of these kittens had alopecia on their shoulders at the final evaluation. It could not be determined if these clinical findings were related to the drug. Histologic examinations of the biopsies were considered to be within normal limits. The body weights varied between the groups but were considered not significantly different by a one-way analysis of variance.

	Mean Body Weight (g)		
Group	**Start**	**End**	**Difference**
I	259	317	59
II	284	322	39

III	279	339	60
IV	282	305	24

Conclusions: 0.01% ivermectin otic suspension did not cause any dermal irritation or inflammation up to 3X the recommended dose. At 5X the recommended dose, scratches on the ears and alopecia on the shoulders were observed.

2. Title: Target Animal Safety Study of a Test Article in the Ears of Approximately Four Week Old Kittens, Laboratory Study # 4868-99

   Purpose: To determine the safety and potential dermal irritation of three levels of ear treatment in approximately 4 week old kittens.

   Investigator: Janice O. Kuhn, Ph.D., D.A.B.T.

   Study Location: Stillmeadow, Inc.
   Sugar Land, Texas 77478-2521

   Animals: 24 kittens (12 males and 12 females), approximately 4 weeks old, 6 kittens per group (3 males and 3 females).

   Dosage Groups: Group I: Untreated control
   Group II: 1X (0.01% ivermectin otic suspension)
   Group III: 3X (0.01% ivermectin otic suspension)
   Group IV: 5X (0.01% ivermectin otic suspension)

   Route of Administration: Topical application into the ear canal.

   Frequency of Treatment: Treated once a day for six consecutive days:
   Group II, 1X Once a day
   Group III, 3X (1X three times)
   Group IV, 5X (1X five times)

   Duration of Study: 13 days

   Parameters measured: A physical exam was performed on day –5. The kittens were observed hourly for the first six hours post-treatment for signs of pharmacologic and/or toxicologic effects and for dermal irritation in the ears. For the remainder of the study, the kittens were observed daily. At Day 13, a biopsy of the external ear canal was obtained and examined histologically for dermal irritation or inflammation. Body weights were recorded on days –12, –1 and 13.

   Results: No pharmacologic or toxicologic effects were recorded during the study. Clinical signs of dermal irritation were not seen in the ears of any of the kittens.

Histologic examinations of the biopsies were all considered to be within normal limits except one kitten (1237F-17M) in the 1X group. This kitten had a single sebaceous gland with a few chronic inflammatory cells at its periphery and was diagnosed as "inflammation chronic, minimal."

The body weights varied between the groups but were considered not clinically significant.

	Mean Body Weight (g)			**Differences**	
	Day -12	Day -1	Day 13	Day 13-Day -12	Day 13-Day -1
Group I	236.5	342.6	464.9	228.4	122.4
Group II	229.7	348.6	463.0	233.3	114.4
Group III	234.4	336.6	456.5	222.1	119.9
Group IV	229.0	335.0	444.4	215.4	109.4

Conclusions: Single or multiple doses of 0.01% ivermectin otic suspension did not cause dermal irritation or inflammation in any of the groups examined up to 5X the recommended dose except for one kitten in the 1X group with histologic evidence of minimal dermal inflammation.

VI. HUMAN SAFETY:

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

Human Warnings are provided on the product label as follows: "Not for human use. Keep out of 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 ACAREXX (0.01% ivermectin) otic suspension for cats and kittens, when used under 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.

Blue Ridge Pharmaceuticals, Inc. has the following patents:

US 4,761,288 expires August, 2005
US 4,897,269 expires January, 2007
US 4,937,078 expires June, 2007

VIII. LABELING (Attached)

a. Package Insert
b. Dispensing Carton
c. Foil Pouch