

DEC 5 2000

**FREEDOM OF INFORMATION SUMMARY**

9328 '01 JAN 22 A6:34

**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**

NADA 141-174

FOIS 1

## Table of Contents

	<u>Page</u>
I. GENERAL INFORMATION:.....	3
II. INDICATIONS FOR USE: .....	3
III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE:.....	3
IV. EFFECTIVENESS: .....	4
LABORATORY DOSE TITRATION/CONFIRMATION STUDY .....	4
CLINICAL FIELD TRIAL .....	5
V. ANIMAL SAFETY: .....	7
VI. HUMAN SAFETY: .....	9
VII. AGENCY CONCLUSIONS: .....	9
VIII. LABELING (ATTACHED).....	10

## **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  
1055 Highway 65  
Rural Hall, NC 27045

Dr. Jan Strother  
N. Alabama Cat & Bird Veterinary  
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.

Group	Mean Body Weight (g)		Difference
	Start	End	
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
<b>Group I</b>	236.5	342.6	464.9	228.4	122.4
<b>Group II</b>	229.7	348.6	463.0	233.3	114.4
<b>Group III</b>	234.4	336.6	456.5	222.1	119.9
<b>Group IV</b>	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

## Package Insert

# ACAREXX™

(0.01% IVERMECTIN)

### Otic Suspension

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

**DESCRIPTION:** Chemical Name: Ivermectin is a mixture of 5-O-demethyl-22,23-dihydroivermectin A<sub>1a</sub> (component B<sub>1a</sub>) and 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)ivermectin A<sub>1b</sub> (component B<sub>1b</sub>). Empirical formula: B<sub>1a</sub> = C<sub>48</sub>H<sub>74</sub>O<sub>14</sub>, B<sub>1b</sub> = C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>. Molecular weight: B<sub>1a</sub> = 875.10, B<sub>1b</sub> = 861.07.

**INDICATIONS:** ACAREXX® (ivermectin) 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.

**HUMAN WARNINGS:** Not for human use. Keep out of reach of children.

**PRECAUTIONS:** The safe use of ACAREXX in cats used for breeding purposes, during pregnancy, or in lactating queens, has not been evaluated.

**ADVERSE REACTIONS:** In approximately 1% of 80 cats and kittens, pain associated with the pinna and vomiting were observed following treatment with ACAREXX.

**DOSAGE:** ACAREXX is administered topically in the ear canal at an ivermectin concentration of 0.01%. 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.

**ADMINISTRATION:** Tear 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. In clinical field trials, ears

were not cleaned and many animals still had debris in their ears at the end of the study. Cleaning the ears prior to administration of ACAREXX is not necessary to provide effectiveness.

**EFFECTIVENESS:** One treatment with ACAREXX was 92% effective in treating adult ear mite (*Otodectes cynotis*) infestations after 7 days in a dose titration/confirmation study. In a well-controlled clinical field trial, one treatment of ACAREXX was 94% effective in clearing cats and kittens of adult ear mite infestations within 7 to 10 days.

**SAFETY:** In two Target Animal Safety studies, ACAREXX was proven to be safe in kittens four weeks of age or older. Four week old kittens were administered ACAREXX at dose rates of 1X, 3X, and 5X the recommended dose for three or six consecutive days and no adverse reactions were observed except one kitten treated at 1X the dose had histologic evidence of minimal, chronic dermal inflammation of the ear. In a well-controlled clinical field trial, ACAREXX was used safely in cats and kittens receiving other frequently used veterinary products such as flea control products, vaccines, anthelmintics, antibiotics, and steroids.

**STORAGE CONDITIONS:** ACAREXX should be stored at temperatures below 86° F (30° C). Protect from freezing.

**HOW SUPPLIED:** ACAREXX is packaged in two polypropylene ampules per foil pouch, which are packaged 12 foil pouches per display carton. Each ampule is filled to deliver 0.5 mL of 0.01% ivermectin otic suspension per ear.

Manufactured for Blue Ridge Pharmaceuticals, Inc.  
Greensboro, NC 27410 USA  
A Subsidiary of IDEXX Laboratories, Inc.

ACAREXX is a trademark of Blue Ridge Pharmaceuticals, Inc.  
©2000 Blue Ridge Pharmaceuticals, Inc.

For technical assistance or to report adverse drug reactions,  
please call 1-800-374-8006.  
For more information visit [www.brpharma.com](http://www.brpharma.com)

NADA 141-174, Approved by FDA

BRP/LS/01/IN/1 06/00  
06-04001-00



Dispensing Carton  
Front and Back

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.

NET CONTENTS: 12 foil pouches containing 2 ampules per pouch. Each ampule contains 0.5 mL of 0.01% ivermectin otic suspension.

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

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

NADA 141-174, Approved by FDA

**ACAREXX™**  
**(0.01% IVERMECTIN)**

*Otic Suspension*



**ACAREXX™**  
**(0.01% IVERMECTIN)**

*Otic Suspension*

FPO lot#  
Exp. date



**ACAREXX™**  
(0.01% IVERMECTIN)

*Otic Suspension*

Dispensing Carton  
Top

**Dispensing Carton  
Bottom**



98-09239-00

**Dispensing Carton  
Right Side**

**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.

Manufactured for Blue Ridge Pharmaceuticals, Inc.  
Greensboro, NC 27410 USA  
A Subsidiary of IDEXX Laboratories, Inc.

ACAREXX is a trademark of Blue Ridge Pharmaceuticals, Inc.  
©2000 Blue Ridge Pharmaceuticals, Inc.



## Dispensing Carton Left Side

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

**DESCRIPTION:** Chemical Name: Ivermectin is a mixture of 5-O-demethyl-22,23-dihydroavermectin A<sub>1a</sub> (component B<sub>1a</sub>) and 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A<sub>1a</sub> (component B<sub>1b</sub>). Empirical formula: B<sub>1a</sub>=C<sub>48</sub>H<sub>74</sub>O<sub>14</sub>, B<sub>1b</sub>=C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>. Molecular weight: B<sub>1a</sub>=875.10, B<sub>1b</sub>=861.07.

**INDICATIONS:** ACAREXX™ (ivermectin) 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.

**WARNINGS:** Not for human use. Keep out of reach of children.

**PRECAUTIONS:** The safe use of ACAREXX in cats used for breeding purposes, during pregnancy, or in lactating queens, has not been evaluated.

**ADVERSE REACTIONS:** In approximately 1% of 80 cats and kittens, pain associated with the pinna and vomiting were observed following treatment with ACAREXX.

**DOSAGE:** ACAREXX is administered topically in the ear canal at an ivermectin concentration of 0.01%. 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.

**STORAGE CONDITIONS:** ACAREXX should be stored at temperatures below 86° F (30° C). Protect from freezing.

Refer to Package Insert for complete prescribing information.

BRP/ILS/01/BX/1 06/00

05-07289-00

# 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.

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

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



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

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

**DOSAGE:** ACAREXX™ (ivermectin) is administered topically in the ear canal at an ivermectin concentration of 0.01%. 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.

**ADMINISTRATION:** Tear 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. In clinical field trials, ears were not cleaned and many animals still had debris in their ears at the end of the study. Cleaning the ears prior to administration of ACAREXX is not necessary to provide effectiveness.

**PRECAUTIONS:** The safe use of ACAREXX in cats used for breeding purposes, during pregnancy, or in lactating queens, has not been evaluated.

**ADVERSE REACTIONS:** In approximately 1% of 80 cats and kittens, pain associated with the pinna and vomiting were observed following treatment with ACAREXX.

Refer to package insert for complete prescribing information.

**NET CONTENTS:** 2 ampules per pouch. Each ampule contains 0.5 mL of 0.01% ivermectin otic suspension.

Manufactured for Blue Ridge Pharmaceuticals, Inc.  
Greensboro, NC 27410 USA  
A Subsidiary of IDEXX Laboratories, Inc.

ACAREXX is a trademark of Blue Ridge Pharmaceuticals, Inc.  
©2000 Blue Ridge Pharmaceuticals, Inc.  
BRP/LS/01/FP/3 3/00 04-04004-00