

# AcuGuard® (spinosad) Chewable Tablets



## ACUGUARD®-Cats (spinosad) Chewable Tablets

For information on dogs, see reverse side.

**Caution:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

### Description:

ACUGUARD (spinosad) is available in four sizes of chewable flavored tablets for oral administration to cats and kittens according to their weight. Each chewable flavored tablet is formulated to provide a minimum spinosad dosage of 22.5 mg/lb (50 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial tetracyclic macrolides. Spinosad contains two major factors, spinosyn A and spinosyn D, derived from the naturally occurring bacterium, *Saccharopolyspora spinosa*. Spinosyn A and spinosyn D have the chemical compositions 2-[(6-deoxy-2,3,4-tri-O-methyl- $\alpha$ -L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione and 2-[(6-deoxy-2,3,4-tri-O-methyl- $\alpha$ -L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione, respectively.

### Indications:

ACUGUARD kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), for one month, on cats and kittens 14 weeks of age and older and two pounds of body weight or greater.

### Dosage and Administration:

ACUGUARD is given orally once a month, at the minimum dosage of 22.5 mg/lb (50 mg/kg).

**Do not use the dosing schedule below when administering ACUGUARD to dogs, as it can result in an overdose.**

#### Dosage Schedule:

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
2 to 4 lbs	90	One
4.1 to 6 lbs	140	One
6.1 to 12 lbs	270	One
12.1 to 24* lbs	560	One

\*Cats over 24 lbs should be administered the appropriate combination of tablets.

Administer ACUGUARD with food for maximum effectiveness.

ACUGUARD is a chewable tablet that can be consumed by cats when offered by the owner just prior to or after feeding. Alternatively, ACUGUARD may be offered in food or administered like other tablet medications. ACUGUARD should be administered at monthly intervals.

If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer ACUGUARD with food and resume a monthly dosing schedule.

Treatment with ACUGUARD may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of flea season. In areas where fleas are common year-round, monthly treatment with ACUGUARD should continue the entire year without interruption.

To minimize the likelihood of flea reinfestations, it is important to treat all animals within a household with an approved flea protection product.

### Contraindications:

There are no known contraindications for the use of ACUGUARD.

### Warnings:

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

### Precautions:

Use with caution with concomitant extra-label use of ivermectin (see ADVERSE REACTIONS).

The safe use of ACUGUARD in breeding, pregnant, or lactating cats has not been evaluated.

### Adverse Reactions:

In a well-controlled US field study, which included a total of 211 cats (139 treated with ACUGUARD and 72 treated with an active topical control once a month for 3 treatments), no serious adverse reactions were attributed to the administration of ACUGUARD.

Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence > 1% within any of the 3 months of observations are presented in the following table. The most frequently reported adverse reaction in cats was vomiting.

#### Percentage of Cats (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	ACUGUARD (n=139)	Active Topical Control (n=72)	ACUGUARD (n=135)	Active Topical Control (n=69)	ACUGUARD (n=132)	Active Topical Control (n=67)
Vomiting	14.4	1.4	14.8	1.4	13.6	4.5
Lethargy	3.6	0.0	0.7	0.0	1.5	1.5
Anorexia	2.2	0.0	0.7	0.0	2.3	1.5
Weight Loss	1.4	0.0	0.0	0.0	3.0	0.0
Diarrhea	1.4	1.4	0.7	2.9	2.3	1.5

Over the 3-month (3-dose) study, vomiting occurred on the day of or the day after at least one dose in 28.1% (39/139) of the cats treated with ACUGUARD and in 2.8% (2/72) of the cats treated with the active topical control. Three of the 139 cats treated with ACUGUARD vomited on the day of or the day after all three doses.

Two cats that received extra-label topical ivermectin on Day -1 of the field study developed lethargy on Day 1 after ACUGUARD administration on Day 0.

For technical assistance or to report suspected adverse drug events, call 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>

### Mode of Action:

The primary target of action of ACUGUARD in insects is an activation of nicotinic acetylcholine receptors (nAChRs). Spinosad does not interact with known binding sites of other nicotinic or GABAergic insecticides such as neonicotinoids, fiproles, milbemycins, avermectins, and cyclodienes. Insects treated with spinosad show involuntary muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosad-induced hyperexcitation results in prostration, paralysis, and flea death. The selective toxicity of spinosad

between insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nAChRs.

### Effectiveness:

In a well-controlled laboratory study, ACUGUARD began to kill fleas 30 minutes after administration and demonstrated 98% effectiveness within 4 hours. ACUGUARD kills fleas before they can lay eggs. In a separate well-controlled laboratory study, ACUGUARD demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 30.

If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment.

In a field study conducted in households with existing flea infestations, flea count reductions of 97.5% were observed one month after the first treatment and 99.3% after three monthly treatments with ACUGUARD. Cats with pre-existing signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis, and pruritus as a direct result of eliminating the fleas.

### Animal Safety:

In a margin of safety study, ACUGUARD was administered orally to 14-week-old kittens at 1X, 3X, and 5X the upper half (75 – 100 mg/kg) of the therapeutic dose band for six monthly dosing intervals 28 days apart. Vomiting was observed across all groups, but was seen with greater frequency in cats in the treated groups; it did not increase with increasing doses. Loose stool was observed in all but the 3X treatment group. Food consumption was decreased in the 5X female cats. ACUGUARD was not associated with clinically significant changes in hematology, clinical chemistry, coagulation, or urinalysis parameters. Cats administered ACUGUARD once monthly for 6 months in the 3X and 5X dose groups demonstrated cytoplasmic vacuolation, consistent with phospholipidosis, in the liver, lung, and adrenal gland. The long term effects of phospholipidosis are unknown. The administration of ACUGUARD was not associated with any clinically significant, gross necropsy or histopathological changes.

In a well-controlled field study, ACUGUARD was administered safely in conjunction with other frequently used veterinary products, including tapeworm anthelmintics, antibiotics, and an approved heartworm preventative containing ivermectin. Hematology and clinical chemistry values were compared pre- and post-study and were unremarkable.

### Storage Information:

Store at 20 to 25°C (68 to 77°F), excursions permitted between 15 to 30°C (59 to 86°F).

### How Supplied:

ACUGUARD is available in four tablet sizes for use in cats: 90, 140, 270 or 560 mg. Each tablet size is available in color-coded packages of 6 tablets.

# ACUGUARD®-Dogs

## (spinosad)

### Chewable Tablets

For information on cats, see reverse side.

**Caution:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**Description:**  
ACUGUARD (spinosad) is available in six sizes of chewable flavored tablets for oral administration to dogs and puppies according to their weight. Each chewable tablet is formulated to provide a minimum spinosad dosage of 13.5 mg/lb (30 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial tetracyclic macrolides. Spinosad contains two major factors, spinosyn A and spinosyn D, derived from the naturally occurring bacterium, *Saccharopolyspora spinosa*. Spinosyn A and spinosyn D have the chemical compositions 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[5-dimethylamino]-tetrahydro-6-methyl-2H-pyran-2-yl[oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7, 15-dione and 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[5-dimethylamino]-tetrahydro-6-methyl-2H-pyran-2-yl[oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, respectively.

**Indications:**  
ACUGUARD kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on dogs and puppies 14 weeks of age and older and 3.3 pounds of body weight or greater.

**Dosage and Administration:**  
ACUGUARD is given orally once a month, at the recommended minimum dosage of 13.5 mg/lb (30 mg/kg).

**Do not use the dosing schedule below when administering ACUGUARD to cats, as it can result in an underdosage.**

*Dosage Schedule:*

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
3.3-4.9 lbs	90	One
5 to 10 lbs	140	One
10.1 to 20 lbs	270	One
20.1 to 40 lbs	560	One
40.1 to 60 lbs	810	One
60.1 to 120* lbs	1620	One

\* Dogs over 120 lbs should be administered the appropriate combination of tablets.

Administer ACUGUARD with food for maximum effectiveness.

ACUGUARD is a chewable tablet and is readily consumed by dogs when offered by the owner just prior to feeding. Alternatively, ACUGUARD may be offered in food or administered like other tablet medications. ACUGUARD should be administered at monthly intervals.

If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer ACUGUARD with food and resume a monthly dosing schedule.

Treatment with ACUGUARD may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of flea season. In areas where fleas are common year-round, monthly treatment with ACUGUARD should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea protection product.

**Contraindications:**  
There are no known contraindications for the use of ACUGUARD.

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

Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with ACUGUARD (see **POST APPROVAL EXPERIENCE**).

**Precautions:**  
ACUGUARD is for use in dogs and puppies 14 weeks of age and older (see **ANIMAL SAFETY**).

Use with caution in breeding females (see **ANIMAL SAFETY**). Use with caution in dogs with pre-existing epilepsy (see **ADVERSE REACTIONS**). The safe use of ACUGUARD in breeding males has not been evaluated.

**Adverse Reactions:**  
In a well-controlled US field study, which included a total of 470 dogs (330 dogs treated with ACUGUARD and 140 dogs treated with an active control), no serious adverse reactions

were observed with ACUGUARD. All reactions were regarded as mild and did not result in any dog being removed from the study.

Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence > 1% within any of the 3 months of observation are presented in the following table. The most frequently reported adverse reaction in dogs in the ACUGUARD and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of ACUGUARD.

Percentage of Dogs (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	ACUGUARD Chewable Tablets (N=330)	Active Topical Control (N=139)*	ACUGUARD Chewable Tablets (N=282)	Active Topical Control (N=124)	ACUGUARD Chewable Tablets (N=260)	Active Topical Control (N=125)
Vomiting	12.7	12.2	7.8	3.2	5.8	4.8
Decreased Appetite	9.1	5.0	2.8	1.6	1.9	0.8
Lethargy	7.6	5.0	3.5	4.0	1.2	0.8
Diarrhea	6.7	5.0	4.3	0.8	1.2	0.0
Cough	3.9	5.0	0.4	2.4	0.0	0.0
Polydipsia	2.4	1.4	0.7	0.0	0.4	0.0
Vocalization	1.8	0.0	0.4	0.0	0.4	0.0
Increased Appetite	1.5	0.0	0.4	0.8	0.4	0.0
Erythema	1.5	0.0	0.4	0.0	0.4	0.0
Hyperactivity	1.2	1.4	0.0	0.0	0.4	0.0
Excessive Salivation	1.2	0.0	0.4	0.0	0.0	0.0

\* This number (n=139) is less than the total number of dogs in the safety population for the active control group (n=140) because one dog joined the study late and was only dosed at Month 3.

In US and European field studies, no dogs experienced seizures when dosed with ACUGUARD at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of ACUGUARD, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

**Post Approval Experience (June 2009):**

The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: *vomiting, depression/lethargy, anorexia, ataxia, diarrhea, pruritus, trembling, hypersalivation and seizures*.

Following concomitant extra-label use of ivermectin with ACUGUARD, some dogs have experienced the following clinical signs: *trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation*.

Post approval experience continues to support the safety of ACUGUARD when used concurrently with heartworm preventatives according to label directions.

For technical assistance or to report suspected adverse drug events, call 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>

**Mode of Action:**  
The primary target of action of ACUGUARD in insects is an activation of nicotinic acetylcholine receptors (nAChRs). Spinosad does not interact with known insecticidal binding sites of other nicotinic or GABAergic insecticides such as neonicotinoids, fiproles, milbemycins, avermectins, and cyclodienes. Insects treated with spinosad show involuntary muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosad-induced hyperexcitation results in prostration, paralysis, and flea death. The selective toxicity of spinosad between insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nAChRs.

**Effectiveness:**  
In a well-controlled laboratory study, ACUGUARD began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. ACUGUARD kill fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with ACUGUARD. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis and pruritus as a direct result of eliminating the fleas.

**Animal Safety:**  
ACUGUARD was tested in pure and mixed breeds of healthy dogs in well-controlled clinical and laboratory studies. No dogs were withdrawn from the field studies due to treatment-related adverse reactions.

In a dose tolerance study, ACUGUARD was administered orally to adult Beagle dogs at average doses of up to 100 mg/kg once daily for 10 consecutive days (16.7 times the maximum recommended monthly dose). Vomiting was seen in 5 of 6 treated dogs during the first 6 days of treatment, usually within 2.5 hours of dosing. Treated females lost weight early in the treatment period, but their weights were similar to control dogs by the end of the 24-day study. ACUGUARD was not associated with any clinically significant changes in hematology, blood coagulation or urinalysis parameters; however, mild elevations in ALT occurred in all dogs treated with ACUGUARD. By day 24, ALT values had returned to near baseline levels. Phospholipidosis (vacuolation) of the lymphoid tissue was seen in all dogs treated with ACUGUARD, the long-term effects of which are unknown.

In a margin of safety study, ACUGUARD was administered orally to 6-week-old Beagle puppies at average doses of 1.5, 4.4, and 7.4 times the maximum recommended dose at 28-day intervals over a 6-month period. Vomiting was observed across all groups, including the control. Increased vomiting was observed at elevated doses, usually within 1 hour following administration. Vomiting at all doses decreased over time and stabilized when puppies were 14 weeks of age. The average daily and total weight gains of treated dogs were smaller than control dogs and were dose dependent. ACUGUARD was not associated with clinically significant changes in hematology, clinical chemistry, coagulation or urinalysis parameters. Phospholipidosis (vacuolation) of the lymphoid tissue was seen in some dogs in the 4.4X group and all dogs in the 7.4X group. The long term effects of phospholipidosis are unknown. Treatment with ACUGUARD was not associated with any other clinically significant adverse clinical observations, gross necropsy or histopathological changes.

In a reproductive safety study, ACUGUARD was administered orally to female Beagles at 1.3 and 4.4 times the maximum recommended therapeutic dose every 28 days prior to mating, during gestation, and during a six-week lactation period. No treatment-related adverse effects were noted for conception rates in the dams, or for mortality, body temperature, necropsy, or histopathology findings for the dams or puppies. One dam from each treatment group experienced early pregnancy loss and one additional high dose dam aborted late term. The treated dams experienced more vomiting, especially at one hour post-dose, than the control dams. Puppies from dams treated at 1.3 times the maximum recommended therapeutic dose had lower body weights than puppies from control dams. Although puppy mortality between treated and control dams was not different, the puppies from the treated dams experienced more lethargy (4.4X group only), dehydration, weakness and felt cold to the touch (4.4X group only) than puppies from control dams.

A pilot study without a control group was conducted to analyze milk from three lactating dogs treated with an experimental formulation of spinosad at 1.5 times the maximum recommended dose administered at day 28 of gestation and 24 hours prior to parturition. The data demonstrated that spinosyns were excreted in the milk of these dogs. Mortality and morbidity were greatest in puppies from the dam with the highest spinosyns level in milk. The spinosad milk: reference plasma exposure ratio calculated from this study ranged from 2.2 to 3.5.

In well-controlled field studies, ACUGUARD was administered safely in conjunction with other frequently used veterinary products, such as vaccines, anthelmintics, antibiotics, steroids, flea and tick control products, anesthetics, NSAIDs, antihistamines, alternative/herbal remedies, shampoos, and prescription diets. Changes in hematology, clinical chemistry and urinalysis values were compared pre- and post-study and were unremarkable.

**Storage Information:**  
Store at 20-25°C (68 -77°F), excursions permitted between 15 to 30°C (59 to 86°F).

**How Supplied:**  
ACUGUARD is available in six tablet sizes for use in dogs: 90, 140, 270, 560, 810 or 1620 mg. Each tablet size is available in color-coded packages of 6 tablets.

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Los Angeles, CA 90064  
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NDC 50386-4221-7	CA4221Y07AMC1
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NDC 50386-4224-7	CA4224Y07AMC1
NDC 50386-4225-7	CA4225Y07AMC1
NDC 50386-4227-7	CA4227Y07AMC1