Lilly Companion Animal Health Technical Bulletin:
Spinosad and the Extra-Label Use of High Dose Ivermectin for the Treatment of Generalized Demodicosis in Dogs

Key Points

- **Many veterinarians employ the use of high extra-label doses of ivermectin to treat nonresponsive demodectic mange and other conditions in dogs.**
- **Published recommendations for this extra-label use can be up to 100X or greater the labeled single monthly dose of 6-12µg/kg for heartworm prevention.**
- **Lilly has received reports in which dogs receiving these extra-label protocols for treatment of demodicosis have developed signs that have typically been reported with mild to moderate ivermectin toxicity, shortly following concurrent administration of Comfortis® (spinosad).**
- **As a result of these reports, Lilly recommends that dogs receiving extra-label doses of ivermectin should not receive concurrent treatment with Comfortis®.**

Treatment of generalized demodectic mange in dogs often involves the use of extremely high doses of ivermectin of up to 100X the recommended monthly dose rate for heartworm prevention. Although safe for use at labeled doses, avermectins can be neurotoxic, and use of these high dose regimens carries substantial risk of causing ivermectin toxicity.

Since the launch of Comfortis® in November 2007, Lilly has received reports in which dogs receiving extra-label high dose ivermectin have developed signs that have typically been reported in the literature with ivermectin toxicity within a short time following administration of a labeled dose of Comfortis®. In these cases, all dogs have recovered with supportive therapy, usually within 24-72 hours.

These reports highlight the need for veterinarians to:

1. Remember that the use of exaggerated doses of most products can result in a lowered margin of safety for patients.

2. Carefully consider the use of any drug simultaneously with extra-label administration of high doses of either ivermectin or other avermectins or milbemycins.

3. Maintain vigilance for signs of unexpected reactions, regardless of whether or not concomitant drugs are used, in dogs being treated in this extra-label manner.

4. Avoid spinosad use in dogs currently receiving these extra-label protocols.

The most common adverse reaction recorded during clinical trials was vomiting. Other adverse reactions were decreased appetite, lethargy or decreased activity, diarrhea, cough, increased thirst, vocalization, increased appetite, redness of the skin, hyperactivity and excessive salivation. For product label, including important safety information, see back page.

The administration of Comfortis® and approved canine formulations of ivermectin at doses labeled for heartworm prevention has been tested and shown to be safe, including in a North American field trial involving over 450 dogs that were required to be on monthly heartworm prevention throughout the three-month study. Laboratory work has found that, even at doses of 5 times the monthly dose of spinosad combined with 10 times the monthly dose of milbemycin oxime in ivermectin-sensitive collies, there were no signs of neurotoxicity (Sherman et al., publication pending). Therefore, the concurrent administration of recommended label doses of spinosad and macrocyclic lactone heartworm preventatives, including ivermectin and milbemycin oxime, has demonstrated a wide safety margin, even when used in dogs carrying the genetic mutation (MDR1) that confers avermectin sensitivity. Thus, Comfortis® is approved for use with labeled doses of heartworm preventatives, and field experience has been consistent with the available safety data when used in this approved manner.

Background Information

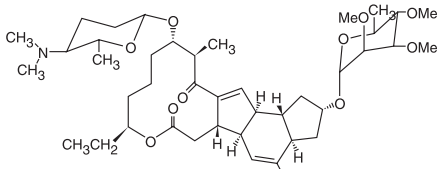
Ivermectin, a macrocylic lactone produced by the fermentation of *Streptomyces avermitilis*, is commonly prescribed by veterinary dermatologists and general practitioners in an extra-label manner for the treatment of canine generalized demodicosis. In these instances, the reported dosage range that has been successful is typically from 450-600 µg/kg/day for weeks to months at a time (Muller and Kirk's *Small Animal Dermatology*, 6th edition, page 472). This **daily** dosage is up to 100X the minimum **monthly** ivermectin dosage recommended for heartworm prevention (6-12 µg/kg/month).

As a reminder, heartworm preventatives should be used at their labeled dose. The introduction of spinosad in dogs already receiving extra-label high doses of avermectins is not recommended, based on these field observations and the fact that such use has not been evaluated in laboratory and/or field studies to date. Additionally, if, in the opinion of the attending veterinarian, the clinical condition of a patient dictates an immediate need for such extra-label therapy, then veterinarians should assess the overall risk versus benefit to the patient and delay Comfortis® administration until completing the extra-label protocol.

COMFORTIS™
(spinosad)
Chewable Tablets

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

Description:
COMFORTIS chewable tablets (spinosad) are available in five chewable flavored tablet sizes 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.



spinosyn A (R=H)
spinosyn D (R=CH_3)

Indications:
COMFORTIS chewable tablets kill fleas and are indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) on dogs for one month.

Dosage and Administration:
COMFORTIS chewable tablets are given orally once a month, at the recommended minimum dosage of 13.5 mg/lb (30 mg/kg).

Recommended Dosage Schedule:

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
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 COMFORTIS chewable tablets with food for maximum effectiveness.

COMFORTIS is a chewable tablet and is readily consumed by dogs when offered by the owner just prior to feeding. Alternatively, COMFORTIS chewable tablets may be offered in food or administered like other tablet medications. COMFORTIS chewable tablets 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 COMFORTIS chewable tablets with food and resume a monthly dosing schedule.

Treatment with COMFORTIS chewable tablets 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 COMFORTIS chewable tablets 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 COMFORTIS chewable tablets.

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

Precautions:
COMFORTIS chewable tablets are 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 COMFORTIS chewable tablets 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 COMFORTIS chewable tablets and 140 dogs treated with an active control), no serious adverse reactions were observed with COMFORTIS chewable tablets. 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 COMFORTIS chewable tablets and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of COMFORTIS chewable tablets.

Percentage of Dogs (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS Chewable Tablets (N=330)	Active Topical Control (N=139[a])	COMFORTIS Chewable Tablets (N=282)	Active Topical Control (N=124)	COMFORTIS 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

[a] 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 COMFORTIS chewable tablets 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 COMFORTIS chewable tablets, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

For technical assistance or to report an adverse drug reaction, call 1-888-545-5973. Additional information can be found at www.comfortis4dogs.com.

Mode of Action:
The primary target of action of COMFORTIS chewable tablets 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, COMFORTIS chewable tablets began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. COMFORTIS chewable tablets 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 COMFORTIS chewable tablets. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis and pruritus as a direct result of eliminating the fleas.

Animal Safety:
COMFORTIS chewable tablets were 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, COMFORTIS chewable tablets were 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. COMFORTIS chewable tablets were 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 COMFORTIS chewable tablets. By day 24, ALT values had returned to near baseline levels. Phospholipidosis (vacuolation) of the lymphoid tissue was seen in all dogs treated with COMFORTIS chewable tablets, the long-term effects of which are unknown.

In a margin of safety study, COMFORTIS chewable tablets were 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. COMFORTIS chewable tablets were 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 COMFORTIS chewable tablets was not associated with any other clinically significant adverse clinical observations, gross necropsy or histopathological changes.

In a reproductive safety study, COMFORTIS chewable tablets were 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, COMFORTIS chewable tablets were 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:
COMFORTIS chewable tablets are available in five flavored tablet sizes: 140, 270, 560, 810 or 1620 mg. Each tablet size is available in color-coded packages of 6 tablets.

NADA 141-277, Approved by FDA

Manufactured for Elanco Animal Health,
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