COMFORTIS™ Chewable Tablets

COMFORTIS™ - 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: COMFORTIS (spinosad) is available in three 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-α-L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5b,6,9,10,11,12,13,14,16a,16b-tetrahydroxy-14-methyl-1H-as-indaceno[3,2-d]oxacyclocodencin-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-2,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetrahydroxy-4,14-dimethyl-1H-as-indaceno[3,2-d]oxacyclocodencin-7,15-dione, respectively.

Indications: COMFORTIS 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 4.1 pounds of body weight or greater.

Dosage and Administration: COMFORTIS 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 COMFORTIS to dogs, as it can result in an overdosage.

Dosing Schedule:

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Spinosad Per Tablet (mg)</th>
<th>Tablets Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 to 6 lbs</td>
<td>140</td>
<td>One</td>
</tr>
<tr>
<td>6.1 to 12 lbs</td>
<td>270</td>
<td>One</td>
</tr>
<tr>
<td>12.1 to 24 lbs</td>
<td>560</td>
<td>One</td>
</tr>
</tbody>
</table>

* Cats over 24 lbs should be administered the appropriate combination of tablets. Administer COMFORTIS with food for maximum effectiveness.

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

Treatment with COMFORTIS 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 should continue the entire year without interruption.

To minimize the likelihood of flea reinfections, 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.

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 COMFORTIS 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 COMFORTIS and 72 treated with an active topical control once a month for 3 treatments), no serious adverse reactions were attributed to the administration of COMFORTIS.

Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at a 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

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMFORTIS (n=139)</td>
<td>COMFORTIS (n=135)</td>
<td>COMFORTIS (n=132)</td>
</tr>
<tr>
<td>Active Topical Control (n=72)</td>
<td>Active Topical Control (n=69)</td>
<td>Active Topical Control (n=67)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

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 COMFORTIS and in 2.8% (2/72) of the cats treated with the active topical control. Three of the 139 cats treated with COMFORTIS 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 COMFORTIS administration on Day 0.

For technical assistance or to report suspected adverse drug events, contact Elanco US Inc. at 1-888-545-5973. For additional information about adverse drug experience reporting for animals, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVetinary/SafetyHealth

Mode of Action: The primary target of action of COMFORTIS 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 cyclodiene. 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 began to kill fleas 30 minutes after administration and demonstrated 98% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. In a separate well-controlled laboratory study, COMFORTIS 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 COMFORTIS. Cats with pre-existing 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: In a margin of safety study, COMFORTIS 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. COMFORTIS was not associated with clinically significant changes in hematology, clinical chemistry, coagulation, or urinalysis parameters. Cats administered COMFORTIS 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 COMFORTIS was not associated with any clinically significant, gross necropsy or histopathological changes.

In a well-controlled field study, COMFORTIS 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: COMFORTIS is available in three tablet sizes for use in cats: 140, 270 or 560 mg. Each tablet size is available in color-coded packages of 6 tablets.
Dosage and Administration: COMFORTIS is given orally once a month, at the minimum dosage of 13.5 mg/lb (30 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial, non-group 4 insecticides. 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-(3,4-dihydro-6-methyl-2H-pyran-2-yl)oxy]-6-methyl-2H-pyran-2,3,4,5,6,7,8,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione and 2-[(6-deoxy-2,3,4-tri-O-methyl-L-lannynopyranosyl)oxy]-13-[5-(3,4-dihydro-6-methyl-2H-pyran-2-yl)oxy]-6-methyl-2H-pyran-2,3,4,5,6,7,8,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, respectively. Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial, non-group 4 insecticides. 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-(3,4-dihydro-6-methyl-2H-pyran-2-yl)oxy]-6-methyl-2H-pyran-2,3,4,5,6,7,8,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione and 2-[(6-deoxy-2,3,4-tri-O-methyl-L-lannynopyranosyl)oxy]-13-[5-(3,4-dihydro-6-methyl-2H-pyran-2-yl)oxy]-6-methyl-2H-pyran-2,3,4,5,6,7,8,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, respectively.

Indications: COMFORTIS 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 5.0 pounds of body weight or greater.

Dosage: Dogs over 120 lbs should be administered the appropriate combination of tablets. Administer COMFORTIS 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 may be offered in food or administered like other tablet medications. COMFORTIS should be administered at monthly intervals. If vomiting occurs within an hour of administration, dose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.

Treatment with COMFORTIS 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 should continue the entire year without interruption.

To minimize the likelihood of flea reintroduction, 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.

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 COMFORTIS (see POST APPROVAL EXPERIENCE).

Precautions: COMFORTIS is for use in dogs and puppies 14 weeks of age and older (see ANIMAL SAFETY). Use with caution in dogs with pre-existing epilepsy (see ADVERSE REACTIONS). The safe use of COMFORTIS in breeding males for the purposes of reproduction 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 and 140 dogs treated with an active control), no serious adverse reactions were observed with COMFORTIS. 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 and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of COMFORTIS.

Percentage of Dogs (%) with Adverse Reactions

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMFORTIS Chewable Tablets (N=330)</td>
<td>Active Topical Control (N=139)</td>
<td>COMFORTIS Chewable Tablets (N=282)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>9.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>7.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Cough</td>
<td>3.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Polyuria</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomitaltion</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Excessive Salivation</td>
<td>1.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*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 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 three weeks, following the second dose of COMFORTIS, 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 adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, anorexia, ataxia, diarrhea, pruritus, trembling, hypersalivation and seizures.

For information on additional extra-label use of ivermectin with COMFORTIS, some dogs have experienced the following common effects: trembling/hitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation.

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

For technical assistance or to report suspected adverse drug events, contact Elanco US Inc. at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact NDC 58198-398-7B-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth

Mode of Action: The primary target of action of COMFORTIS in insects is an activation of nicotinic acetylcholine receptors (nACHRs). Spinosad does not interact with known insecticidal binding sites of other nicotinic or non-nicotinic neurotransmitter receptors in insects.

Effectiveness: In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. COMFORTIS 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 99.9% were observed over the course of 3 months with treatments of COMFORTIS. Dogs with signs of flea allergy dermatitis showed improvement in clinical signs and pruritus within 14 weeks of age, a period of time that correlates with adult flea death. The selective toxicity of spinosad towards insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nACHRs.

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

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

NADA #141-277, Approved by the FDA

Manufactured for:

Elanco US Inc.

UMM, Indiana 46140

1-800-545-5973

www.comfortis.com

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CA4222

NDC 58198-4223-6

CA4223

NDC 58198-4224-6

CA4224

NDC 58198-4225-6

CA4225

NDC 58198-4227-6

CA4227

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