Chewable Tablets

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

Description: TRIFEXIS (spinosad and milbemycin oxime) is available in five sizes for oral administration to dogs and puppies according to their respective body weight. Chewable tablets are formulated to provide a minimum spinosad dose of 13.5 mg/lb (30 mg/kg) and a minimum milbemycin oxime dose of 0.2 mg/lb (0.5 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 C41H65NO10 and C42H67NO10, respectively. Milbemycin oxime is a macrocyclic lactone antihelmintic, containing two major factors, A3 and A4 of milbemycin oxime. The approximate ratio of A3/A4 is 20:80. Milbemycin A3 5-oxime has the chemical composition of C25H35NO5 and milbemycin A4 5-oxime has the chemical composition of C25H35NO5.

Indications: TRIFEXIS is indicated for the prevention of heartworm disease (Dirofilaria immitis), and the treatment and control of adult hookworm (Ancylostoma caninum), adult roundworm (Toxocara canis and Toxascaris leonina) and adult whipworm (Trichus vulpis) infections in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater.

Dosage and Administration: TRIFEXIS should, unless otherwise stated, be given orally, once a day at the minimum dosage of 13.5 mg/lb (30 mg/kg) spinosad and 0.2 mg/lb (0.5 mg/kg) milbemycin oxime body weight. For heartworm prevention, give once monthly for at least 3 months after exposure to mosquitoes (see EFFECTIVENESS).

Average Monthly Rate (%) of Dogs With Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TRIFEXIS Chewable Tablets*</th>
<th>Active Control Tablets*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>6.13</td>
<td>3.08</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4.00</td>
<td>4.91</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2.63</td>
<td>1.54</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.25</td>
<td>1.54</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1.47</td>
<td>1.45</td>
</tr>
<tr>
<td>Skin Reddening</td>
<td>1.37</td>
<td>1.26</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1.27</td>
<td>1.35</td>
</tr>
<tr>
<td>Pinnal Reddening</td>
<td>1.18</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*In 176 dogs

In the US field study, one dog administered TRIFEXIS experienced a single mild seizure 2 1/2 hours after receiving the second monthly dose. The dog remained enrolled and received four additional monthly doses after the event and completed the study without further incident. Following co-concomitant-label use of ivermectin with spinosad alone, a component of TRIFEXIS, some dogs have experienced the following clinical signs: trembling/twitching, salvation/shoeling, seizures, ataxia, mydriasis, blindness and disorientation. Spinosad alone has been shown to be safe when administered concurrently with other heartworm preventives and treatments.

In US and European field studies, no dogs experienced seizures when dosed with spinosad alone 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 spinosad, 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 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-FFA-VETS or www.fda.gov/reportanimal

Post-Marketing Experience (Mar 2012): 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, pruritis, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening.

Mode of Action: The primary target of action of spinosad, a component of TRIFEXIS, is an activation of nicotinic acetylcholine receptors (nAChRs) in insects. 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 hyporeactivity results in prostration, paralysis and death. The selective toxicity of spinosad between insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nAChRs.

Milbemycin oxime, a component of TRIFEXIS, acts by binding to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells. Increased permeability by the cell membrane to chloride ions causes hyperpolarization of affected cells and subsequent paralysis and death of the host. The stereoselective series of parasaccharine oximes exert an astro- and neuroprotective effect on various paraoximes, notably gamma amino butyric acid (GABA).

Effectiveness: Heartworm Prevention: In a well-controlled laboratory study, TRIFEXIS was 100% effective against induced heartworm infections when administered for 3 consecutive monthly doses. Two consecutive monthly doses did not provide 100% effectiveness against heartworm infection. In another well-controlled laboratory study, a single dose of TRIFEXIS was 100% effective against induced heartworm infections.

In a well-controlled six-month US field study conducted with TRIFEXIS, no dogs were positive for heartworm infection as determined by heartworm antigen testing performed at the end of the study and again three months later.

Flea Treatment and Prevention: In a well-controlled laboratory study, TRIFEXIS demonstrated 100% effectiveness on the first day following treatment and 100% effectiveness on Day 30. In a well-controlled laboratory study, spinosad, a component of TRIFEXIS, began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. Spinosad, a component of TRIFEXIS, kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dosing due to the disruption of emergence of adult fleas from 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 spinosad alone. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pruritus and pruritus as a direct result of eliminating the fleas.

Treatments and Control of Intestinal Nematode Infections: In well-controlled laboratory studies, TRIFEXIS was ≥90% effective in removing naturally and experimentally induced adult roundworm, hookworm and whipworm infections.

Effectiveness of TRIFEXIS as a Co-Treatment with Heartworm Preventatives: In a field study of client-owned dogs where 175 dogs were each offered TRIFEXIS once a month for 6 months, dogs voluntarily consumed 54% of the doses when offered plain as if a treat, and 33% of the doses when offered in or on food. The remaining 13% of doses were administered like other tablet medications.

Animal Safety: TRIFEXIS 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 margin of safety study, TRIFEXIS was administered orally to 8-week-old Beagle puppies at doses of 1, 3, and 5 times the upper half of the therapeutic dose band, every 28 days for 6 dosing periods. Vomiting was seen in all groups including control animals with similar frequency. Adverse reactions seen during the course of the study were salivation, tremors, decreased activity, coughing and vocalization.

Body weights were similar between control and treated groups throughout the study. Treatment with TRIFEXIS was not associated with any clinically significant hematology, clinical chemistry or gross necropsy changes. One 5X dog had minimal glomerular liposiderosis observed microscopically. The clinical relevance of this finding is unclear as the lipid staining is often associated with normal aging. Plasma spinosyn A, spinosyn D, milbemycin A3 5-oxime and milbemycin A4 5-oxime concentrations increased throughout the study. At each dosing period, plasma spinosyn A and spinosyn D concentrations were greater than proportional across the dose range 1 to 5X.

Purchase of W1cPA102948XCA4332, CA4333, CA4334, CA4335, CA4336

Greenfield, IN 46140

Visit www.TRIFEXIS.com

CA4332, CA4333, CA4334, CA4335, CA4336

PA102948X
Plasma concentrations of spinosad and milbemycin oxime indicate that expected systemic exposures were achieved throughout the study.

In an avermectin-sensitive Coleus dog study, TRIFEXIS was administered orally at 1, 3, and 5 times the upper half of the recommended therapeutic dose band every 28 days. No signs of avermectin sensitivity were observed after administration of TRIFEXIS during the study period to avermectin-sensitive Coleus dogs. The adverse reactions observed in the treatment groups were vomiting and diarrhea. Body weights in all treatment groups were comparable to the control group. Hematology and clinical chemistry parameters showed no clinically significant changes from study start to end, and all dogs were considered healthy throughout the study.

In your dog's Breeder program you may administer TRIFEXIS orally at 1, 3, and 5 times the upper half of the therapeutic dose band to Beagle dogs with adult heartworm infections and circulating microfilariae, every 28 days for 3 treatments. Vomiting was observed in one dog in the 1X group, in three dogs in the 3X group, and in one dog in the 5X group. All but one incident of vomiting was observed on the treatment day during the first treatment cycle. The vomiting was mild and self-limiting. Hematologically-normal reactions were not observed in any of the treatment groups. Microfilaria counts decreased with treatment.

In a reproductive safety study, TRIFEXIS was administered orally to female dogs at 1 and 3 times the upper half of the therapeutic dose band every 28 days prior to mating, during gestation and during a six-week lactation period. Dogs with confirmed fetal heartbeats on ultrasound examination were evaluated for reflex thrust of the heart. Reflexes were seen in the control and milbemycin oxime treatment and the 1X and 3X dogs that did not become pregnant, the specific pup malformations and the unthriftliness in 1X group pup are unknown. The incidence of cleft palate is not unexpected based on the historical data collected at the breeding site.

In a margin of safety study with spinosad alone, 6-week old Beagle puppies were administered administered average body weights between 1.5 to 4.4 pounds. No treatment-related adverse reactions or signs of avermectin toxicosis were noted for adult females. Adult females in the 3X group lost weight during the 6-week pre-mating period, while control group females gained weight during that time. The body weights of the treated groups were comparable to the control group during gestation and post-partum phases of the study. Gestation length, litter average body weight, litter size, stillbirths, pup survival and the proportion of pups with malformations were comparable between treated and control dam groups. Malformations in the 1X group included a pup with cleft palate and a littermate with anophthalmia, fused single nares, misshapen palate, hydrocephalus, emphysema and malpositioned testes; a pup with a malformation of the anterior tip of the urinary bladder and umbilical blood vessel; and a pup with patent ductus arteriosus (PDA). Malformations in the 3X group included three littersmates with PDA. Malformations in the control group included a pup with a malformed sternum and a pup with PDA and a malpositioned superior vena cava. Clinical findings in pups of the treated groups were comparable to the control group except for one 1X group pup that was smaller and less coordinated than its littersmates and had tremors when examined shortly before the experiment began. Response to administration of milbemycin oxime oxime treatment and the 1X and 3X dogs that did not become pregnant, the specific pup malformations and the unthriftiness 1X group pup are unknown. The incidence of cleft palate is not unexpected based on the historical data collected at the breeding site.

In an avermectin-sensitive Collie dog study, TRIFEXIS was administered orally at 1, 3, and 5 times the upper half of the recommended dose at 28-day intervals over a 6-month period. Vomiting was observed across all treatments, including controls, and was observed at an increased rate at elevated doses. Vomiting most often occurred 1 hour following administration and decreased over time and stabilized when puppies reached 14 weeks of age.


Dosage and Administration: TRIFEXIS is available in five tablet sizes. Each tablet size is available in color-coded packages of 6 tablets.

- 5-10 lbs (140 mg spinosad and 2.3 mg milbemycin oxime)
- 10-20 lbs (270 mg spinosad and 4.5 mg milbemycin oxime)
- 20-40 lbs (560 mg spinosad and 9.3 mg milbemycin oxime)
- 40-60 lbs (810 mg spinosad and 13.5 mg milbemycin oxime)
- Over 60 lbs (1,260 mg spinosad and 27 mg milbemycin oxime)

Approved by FDA under NADA # 141-321

Manufactured: Elanco US Inc.
Greenfield, IN 46140

Revised: May 2020

Information for Dog Owners

Your veterinarian has chosen to prescribe TRIFEXIS Chewable tablets for the prevention of heartworm disease (Dirofilaria immitis), to kill fleas and for the prevention and treatment of flea infestations (Ctenocephalides felis), and the treatment and control of adult hookworm (Ancylostoma caninum), adult roundworm (Toxocara canis and Toxascaris leonina) and adult whipworm (Trichuris vulpis) infections in dogs and puppies 8 weeks of age and older and 5 pounds of body weight or greater. Controlling these parasites is very important to the health of your dog. Please read this leaflet, which describes the proper use of TRIFEXIS. If you have any questions about this information, please consult your veterinarian. Additional information can be found at www.trifexis.com.

What is TRIFEXIS?

TRIFEXIS is a chewable, flavored tablet that you give orally to your dog once-a-month to kill fleas, to prevent flea infestations, to treat and control hookworms, whipworms and roundworms, and to prevent heartworm disease. TRIFEXIS is for monthly use in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater. If you do not administer TRIFEXIS monthly throughout the year, the final dose must be given no fewer than three months following the last exposure to mosquitoes.

Why has your veterinarian prescribed TRIFEXIS?

Your veterinarian has prescribed TRIFEXIS as a way of preventing your dog from developing problems caused by infection with three commonly occurring parasite categories. Heartworm infection can make dogs very sick and can even be fatal. This parasite is spread to dogs by mosquitoes. TRIFEXIS can prevent flea infestations, which is an important factor for the prevention of heartworm disease. TRIFEXIS is for monthly use in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater. If you do not administer TRIFEXIS monthly throughout the year, the final dose must be given no fewer than three months following the last exposure to mosquitoes.

Will TRIFEXIS kill heartworms?

TRIFEXIS prevents heartworm disease by killing certain stages that develop after an infected mosquito bites a dog. As with other heartworm preventative, TRIFEXIS does not kill adult heartworms.

Speak to your veterinarian about treatment options if your dog is diagnosed with an adult heartworm infection.

Will my dog still need to be tested for heartworm infection while taking TRIFEXIS?

You should tell your veterinarian about the frequency of heartworm testing while your dog is taking TRIFEXIS.

How do I switch to TRIFEXIS from another heartworm preventative?

Follow the advice of your veterinarian about switching heartworm preventative.

What should I discuss with my veterinarian regarding TRIFEXIS for my dog?

You should discuss with your veterinarian the type of TRIFEXIS that would be appropriate for your dog, based on your dog's health status, prior medical history and underlying health conditions, and the medical and veterinary history of your dog. Your veterinarian will determine the best possible treatment plan for your dog.

Is it safe to give my dog TRIFEXIS?

TRIFEXIS has been demonstrated to be safe in pure and mixed breeds of healthy dogs when used according to label directions for dogs and puppies 8 weeks of age and older and 5 pounds of body weight or greater. You should discuss the use of TRIFEXIS with your veterinarian prior to use if your dog has a history of epilepsy (seizures). Puppies less than 14 weeks of age may experience a higher rate of vomiting.

Is it safe to give my breeding dogs TRIFEXIS?

TRIFEXIS has been demonstrated to be safe in pure and mixed breeds of healthy dogs when used according to label directions for dogs and puppies 8 weeks of age and older and 5 pounds of body weight or greater. You should discuss the use of TRIFEXIS with your veterinarian prior to use if your dog has a history of epilepsy (seizures). Puppies less than 14 weeks of age may experience a higher rate of vomiting.

Will TRIFEXIS kill fleas?

In a laboratory study of spinosad alone, an active ingredient of TRIFEXIS, spinosad started to kill fleas within 30 minutes and killed 100% of the fleas within 4 hours. TRIFEXIS kills fleas before they can lay eggs.

Does seeing fleas on my dog mean that the treatment is not working?

TRIFEXIS kills fleas before they can lay eggs when used monthly according to the label directions. Remember that all animals in the household should be treated with an approved flea product to help control the flea population.

Can other medications be given while my dog is taking TRIFEXIS?

Ask your veterinarian about the use of TRIFEXIS prior to use in breeding females. The safe use of TRIFEXIS in male dogs intended for breeding has not been evaluated.

What side effects might occur with TRIFEXIS?

Like all medications, sometimes side effects may occur. In some cases, dogs vomited after receiving TRIFEXIS. To ensure heartworm prevention, observe your dog for one hour after administration. If vomiting occurs within an hour of administration, redose with another full dose. During field studies, no severe or prolonged vomiting occurred. Additional adverse reactions observed in the clinical studies were itching, decreased activity, diarrhea, inflammation of the skin, redness of the skin, decreased appetite and redness of the ear. All reactions were regarded as mild. Since the introduction of TRIFEXIS, additional side effects reported are trembling/shaking, ataxia, seizures and hyperalgesia.

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Can other medications be given while my dog is taking TRIFEXIS?

Yes, TRIFEXIS has been given safely with a wide variety of products and medications. Your veterinarian should be made aware of all products that you administer and/or intend to administer to your dog.

How should TRIFEXIS be stored?

Store at 68-77°F (20-25°C). Temporary periods of time outside this range between 59-86°F (15-30°C) are permitted. www.trifexis.com

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