Intestinal Nematode Treatment and Control:
TRIFEXIS also provides treatment and control of roundworms (T. canis, T. leonina), hookworms (A. caninum) and whipworms (T. vulpis). Dogs may be exposed to and can become infected with roundworms, whipworms and hookworms throughout the year, regardless of season or climate. Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

Contraindications:
There are no known contraindications to the use of TRIFEXIS.

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 spinosad alone, a component of TRIFEXIS (see ADVERSE REACTIONS).

Precautions:
Treatment with fewer than 3 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see EFFECTIVENESS).

Prior to administration of TRIFEXIS, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. TRIFEXIS is not effective against adult D. immitis. While the number of circulating microfilariae may decrease following treatment, TRIFEXIS is not indicated for microfilariae clearance (see ANIMAL SAFETY).

Mild, transient hypersensitivity reactions manifested as labored respiration, vomiting, salivation and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Use with caution in breeding females (see ANIMAL SAFETY). The safe use of TRIFEXIS in breeding males has not been evaluated.

Use with caution in dogs with pre-existing epilepsy (see ADVERSE REACTIONS).

Puppies less than 14 weeks of age may experience a higher rate of vomiting (see ANIMAL SAFETY).

Adverse Reactions:
In a well-controlled US field study, which included a total of 352 dogs (176 treated with TRIFEXIS and 176 treated with an active control), no serious adverse reactions were attributed to administration of TRIFEXIS. All reactions were regarded as mild.

Over the 180-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence >1% (average monthly rate) within any of the 6 months of observation are presented in the following table. The most frequently reported adverse reaction in dogs in the TRIFEXIS group was vomiting.

Average Monthly Rate (%) of Dogs With Adverse Reactions:

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Spinosad Per Tablet (mg)</th>
<th>Milbemycin oxime Per Tablet (mg)</th>
<th>Tablets Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 10 lbs</td>
<td>140</td>
<td>2.3</td>
<td>One</td>
</tr>
<tr>
<td>10.1 to 20 lbs</td>
<td>270</td>
<td>4.5</td>
<td>One</td>
</tr>
<tr>
<td>20.1 to 40 lbs</td>
<td>560</td>
<td>9.3</td>
<td>One</td>
</tr>
<tr>
<td>40.1 to 60 lbs</td>
<td>810</td>
<td>13.5</td>
<td>One</td>
</tr>
<tr>
<td>60.1 to 120 lbs</td>
<td>1620</td>
<td>27</td>
<td>One</td>
</tr>
<tr>
<td>Over 120 lbs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Administer TRIFEXIS with food for maximum effectiveness. To ensure heartworm prevention, owners should observe the dog for one hour after dosing. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed and a monthly interval between doses is exceeded, then immediate administration of TRIFEXIS with food and resumption of monthly dosing will minimize the opportunity for the development of adult heartworm infections and flea reinfestations.

Heartworm Prevention:
TRIFEXIS should be administered at monthly intervals beginning within 1 month of the dog’s first seasonal exposure and continuing until at least 3 months after the dog’s last seasonal exposure to mosquitoes (see EFFECTIVENESS). TRIFEXIS may be administered year round without interruption. When replacing another heartworm preventative product, the first dose of TRIFEXIS should be given within a month of the last dose of the former medication.

Flea Treatment and Prevention:
Treatment with TRIFEXIS may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of the flea season. In areas where fleas are common year-round, monthly treatment with TRIFEXIS 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.
spinosyn D concentrations were greater than proportional across the dose range 1 to 5X. Concentrations increased throughout the study. At each dosing period, plasma spinosyn A and milbemycin oxime were observed microscopically. The clinical relevance of this finding is unknown.

Body weights were similar between control and treated groups throughout the study. Vomiting, depression/lethargy, pruritus, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening were recorded. One 5X dog had minimal glomerular lipidosis.

Treatment with TRIFEXIS was not associated with any clinically significant hematology, clinical chemistry or gross necropsy changes. One 5X dog had minimal glomerular lipidosis.

TRIFEXIS was tested in pure and mixed breeds of healthy dogs in well-controlled clinical and field studies. Treatment with TRIFEXIS was not associated with any clinically significant hematology, clinical chemistry or gross necropsy changes. One 5X dog had minimal glomerular lipidosis.

TRIFEXIS is a flavored chewable tablet. In a field study of client-owned dogs where 175 dogs were dosed orally at 1, 3, and 5 times the upper half of the recommended therapeutic dose range every 28 days, no signs of avermectin sensitivity were observed after administration of TRIFEXIS during the study period to avermectin-sensitive Collie dogs.

In an avermectin-sensitive Collie dog study, TRIFEXIS was administered orally at 1, 3, and 5 times the upper half of the recommended therapeutic dose range every 28 days. No signs of avermectin sensitivity were observed after administration of TRIFEXIS during the study period to avermectin-sensitive Collie dogs.

In a heartworm positive safety study, TRIFEXIS was administered 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. Hypersensitivity reactions were not observed in any of the treatment groups. Microfilariae 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 reproductive safety. One 3X and one 1X group female did not become pregnant. No treatment-related adverse reactions or signs of avermectin toxicity 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-parturition phases of the study. Gestation length, litter average body weight, litter size, stillborn pups, 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, omphalocele 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 littermates 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 littermates and had tremors when excited. The relationship between spinosad and milbemycin oxime treatment and the 1X and 3X dogs that did not become pregnant, the specific pup malformations and the unthirty 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 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 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.

Post Approval 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, pruritus, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening.

TRIFEXIS™
(spinosad + milbemycin oxime)
Chewable Tablets

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Storage Information:

How Supplied:
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)
10.1-20 lbs (270 mg spinosad and 4.5 mg milbemycin oxime)
20.1-40 lbs (560 mg spinosad and 9.3 mg milbemycin oxime)
40.1-60 lbs (810 mg spinosad and 13.5 mg milbemycin oxime)
60.1-120 lbs (1620 mg spinosad and 27 mg milbemycin oxime)

NADA 141-321. Approved by the FDA

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Greenfield, IN 46140
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NDC 58198-4336-6

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