Advantage Multi Dogs
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. WARNING: DO NOT ADMINISTER THIS PRODUCT ORALLY. For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings, and Adverse Reactions, for more information.)
Product Satisfaction Guaranteed.

Elanco Animal Health stands behind our range of safe and effective products. We are committed to helping keep pets healthy and to protect them from internal and external parasites. We are proud to support our canine parasiticide portfolio with our Canine Parasiticides Satisfaction Guarantee.

Purchase Requirements
The Satisfaction Guarantee is available to any individual who has purchased Credelio, Interceptor Plus, Trifexis, Advantage Multi for Dogs, Interceptor*, or Comfortis* from a veterinary clinic or with a veterinarian’s prescription from an Elanco approved online distributor and has valid receipt or proof of purchase. Proof of prescription and purchase is required.

Contact Information
If you or your clients have questions regarding the Elanco canine parasiticide portfolio or the Satisfaction Guarantee, please contact our Product & Veterinary Support team at 1-888-545-5973.

Guarantee qualification is subject to eligibility requirements outlined in this document. Elanco reserves the right to perform a complete review of information provided for any satisfaction guarantee request herein, with the ability to accept or deny in full or in part any claim in its sole discretion.

* Applies in the use of dogs only.

Advantage Multi Dogs
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Satisfaction Guarantee from the Brands You Trust

**Credelio**
- Designed to be gentle on dogs and tough on ticks and fleas.
- Labeled to kill ticks and fleas fast and safe for dogs and puppies 8 weeks and older, weighing 4.4 pounds or more.

**Trifexis**
- 3-in-1 parasite protection against fleas and heartworm disease.
- Treats and controls hookworms, roundworms and whipworms.
- Safe for dogs and puppies 8 weeks and older and 5 pounds or more.

**Comfortis**
- A monthly, chewable tablet that kills fleas fast and prevents flea infestations on dogs for a full month. It starts working in just 30 minutes and kills 98% or more fleas within 4 hours.** Safe for dogs and puppies 14 weeks and older, weighing 5 pounds or more.

**Interceptor**
- Prevents heartworm disease in dogs. Interceptor controls adult hookworms and removes and controls adult roundworm and whipworm infections in dogs and puppies. This monthly, chewable tablet is safe and effective for dogs and puppies as young as 4 weeks of age and 2 pounds of body weight or greater.

For Important Safety Information please see pages 6 and 7.

**Data from two laboratory studies conducted in different locations using different cats and strains of fleas.** *Interceptor and Comfortis Product guarantee applies in the use of dogs only.

Advantage Multi Dogs
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Heartworm Disease

Interceptor Plus, Trifexis, Advantage Multi for dogs, and Interceptor* are indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. Advantage Multi for dogs is indicated for the treatment of *Dirofilaria immitis* circulating microfilariae.

**COMPENSATION**

- In the event a dog develops heartworm disease, Elanco will provide:
  - Reimbursement up to $1,500 for the reasonable treatment costs associated with diagnosis of heartworm disease
  - 1 year’s supply of Interceptor Plus, Trifexis, Interceptor*, or Advantage Multi for dogs

**ELIGIBILITY REQUIREMENTS**

- Product was used, at all times, according to label directions
- Dogs who started heartworm protection at 4 months of age or older must have a negative heartworm antigen test at least 6 months after initiation of Interceptor Plus, Trifexis, Interceptor*, or Advantage Multi for dogs
- If one or more doses is missed, a negative heartworm antigen retest is required at least 6 months after the product is restarted to rule out infection during the window of susceptibility due to the missed dose(s)
- Confirmation of heartworm-positive status by two separate blood samples using at least two different brands of antigen tests are required to document heartworm positive status
- Households with five or more dogs may not be eligible
- The American Heartworm Society (AHS) and the Companion Animal Parasite Council (CAPC) recommend annual testing and year-round heartworm disease prevention in dogs**1,2**

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Hookworms, Roundworms, Whipworms, and Tapeworms

Interceptor Plus, Trifexis, Advantage Multi for dogs and Interceptor* are indicated for treatment and control of adult hookworm (*Ancylostoma caninum*), adult roundworm (*Toxocara canis* and *Toxascaris leonina*), and adult whipworm (*Trichuris vulpis*) infections. Interceptor Plus is indicated for the treatment and control of adult tapeworms (*Taenia pisiformis, Echinococcus multiocularis, Echinococcus granulosus* and *Dipylidium caninum*).

Neither Trifexis, Advantage Multi for Dogs, nor Interceptor* are effective in treating and/or controlling tapeworms in dogs and puppies. However, to support our customers, infections with these parasites are also covered under this Satisfaction Guarantee.

**COMPENSATION**

- In the event that a dog tests positive for a hookworm, roundworm, whipworm or tapeworm infection, Elanco will reimburse the veterinary hospital for the cost of a fecal test and up to $100 in costs related to treatment

**ELIGIBILITY REQUIREMENTS**

- Product was used according to label directions within month prior to claim

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* Applies in the use of dogs only.
### Fleas

Credelio, Trifexis, Advantage Multi for dogs, and Comfortis* kill fleas and they are indicated for the treatment and/or prevention of flea infestations (*Ctenocephalides felis*).

**COMPENSATION**
- In the event a dog develops a flea infestation, Elanco will provide:
  - Product replacement

**ELIGIBILITY REQUIREMENTS**
- Product was used according to label directions for a minimum of 30 days prior to the claim
- All other pets in the household must also be treated with an approved flea protection product

### Ticks

Credelio is indicated for the treatment and control of *Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick) and *Rhipicephalus sanguineus* (brown dog tick) infestations.

**COMPENSATION**
- In the event that a dog does not show signs of treatment and control of the described ticks, Elanco will provide:
  - A refund of the purchased product, or
  - Product replacement

**ELIGIBILITY REQUIREMENTS**
- Product was used according to label directions for a minimum of 30 days prior to the claim
- All other dogs in the household must also be treated with an approved tick control product

### Lyme Disease

**COMPENSATION**
- In the event a dog tests positive for *Borrelia burgdorferi* and is not showing clinical signs of Lyme disease, Elanco will reimburse for reasonable and customary diagnostics and treatment as determined reasonably necessary by Elanco
  - If a dog is showing clinical signs, Elanco will support additional diagnostics and treatment costs up to $5,000

**ELIGIBILITY REQUIREMENTS**
- Credelio\(^1\) was used according to label directions
- Dog must test negative for *Borrelia burgdorferi* within 1 month of starting treatment with Credelio\(^1\) and have a negative test yearly thereafter
- Client must demonstrate that the dog received continuous protection with Credelio\(^1\) (purchase history may be required) from the date of the negative *Borrelia burgdorferi* test through the claim date

\(^1\) Credelio is not labeled for the prevention of Lyme disease.
Tics cont.

Lyme Disease + Elanco TruCan Lyme Vaccination

COMPENSATION

- In the event a dog tests positive for *Borrelia burgdorferi*, has clinical signs of Lyme disease and is properly immunized against Lyme disease with an Elanco TruCan Lyme vaccine, coverage increases up to $10,000

ELIGIBILITY REQUIREMENTS

To qualify for additional benefits from the Elanco Vaccine Support Guarantee:

- Credelio® was used according to label directions
- Client must demonstrate that the dog received continuous protection with Credelio® (purchase history may be required) from the date of the negative *Borrelia burgdorferi* antibody test through the claim date
- Negative *Borrelia burgdorferi* test within 1 month of a dog starting Credelio and positive confirmatory test indicating exposure to Lyme (*Borrelia burgdorferi*)
- Dog was vaccinated with an Elanco TruCan Lyme vaccine within the last 15 months

1 Credelio® is not labeled for the prevention of Lyme disease.

Indications and Important Safety Information

**Trifexis®** (spinosad + milbemycin oxime)

**Indications:** Trifexis prevents heartworm disease. Trifexis kills fleas and prevents flea infestations, and treats and controls adult hookworm, roundworm and whipworm infections in dogs and puppies 8 weeks and older and 5 pounds or more.

**Important Safety Information:** The use of ivermectin at higher than FDA-approved doses at the same time as Trifexis can result in serious side effects. Treatment with fewer than three monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention. Prior to administration of Trifexis, dogs should be tested for existing heartworm infection. Use with caution in breeding females. The safe use of Trifexis in breeding males has not been evaluated. Use with caution in dogs with pre-existing epilepsy. The most common adverse reactions reported are vomiting, decreased activity, itching, decreased appetite, and diarrhea. 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. Puppies less than 14 weeks of age may experience a higher rate of vomiting. For complete safety information, please see [Trifexis product label](#) or ask your veterinarian.

**Interceptor®** (milbemycin oxime)

**Indications:** Interceptor® (Milbemycin oxime) prevents heartworm disease and controls adult hookworms and removes/controls adult roundworm and hookworm infections. Approved for use in dogs and puppies 4 weeks of age and older and 2 pounds of body weight or greater.

**Important Safety Information:** Dogs should be tested for heartworm infection prior to use. In a small percentage of treated dogs, digestive and neurologic side effects may occur. Please see [full product information](#).

**Interceptor® Plus** (milbemycin oxime + praziquantel):

**Indications:** Interceptor Plus prevents heartworm disease and treats and controls adult roundworm, hookworm, whipworm, and tapeworm infections in dogs and puppies 6 weeks or older and 2 pounds or greater.

**Important Safety Information:** Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention. Prior to administration of Interceptor Plus, dogs should be tested.
for existing heartworm infections. The safety of Interceptor Plus has not been evaluated in dogs used for breeding or in lactating females. The following adverse reactions have been reported in dogs after administration of milbemycin oxime or praziquantel: vomiting, diarrhea, decreased activity, incoordination, weight loss, convulsions, weakness, and salivation. For complete safety information, please see Interceptor Plus product label or ask your veterinarian.

**Comfortis® (spinosad)**

**Indications:** Comfortis kills fleas and prevents and treats flea infestations for one month on dogs and puppies 14 weeks of age and older and 5 pounds or greater.

**Important Safety Information:** Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with Comfortis. Use with caution in breeding females and dogs with pre-existing epilepsy. The safe use of Comfortis in breeding males has not been evaluated. The most common adverse reactions reported were vomiting, decreased activity, decreased appetite, incoordination, diarrhea, itching, trembling, excessive salivation, and seizures. Post approval experience continues to support the safety of Comfortis when used concurrently with heartworm preventives according to label directions. For complete safety information, please see Comfortis product label or ask your veterinarian.

**Credelio® (lotilaner)**

**Indications:** Credelio kills adult fleas and is indicated for the treatment and prevention of flea infestations and treatment and control of tick infestations (lone star tick, American dog tick, black-legged tick, and brown dog tick) for one month in dogs and puppies 8 weeks and older and 4.4 pounds or greater.

**Important Safety Information:** Lotilaner is a member of the isoxazoline class of drugs. This class has been associated with neurologic adverse reactions including tremors, incoordination, and seizures. Seizures have been reported in dogs receiving this class of drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders. The safe use of Credelio in breeding, pregnant or lactating dogs has not been evaluated. The most frequently reported adverse reactions are weight loss, elevated blood urea nitrogen, increased urination, and diarrhea. For complete safety information, please see Credelio product label or ask your veterinarian.

**Advantage Multi® for Dogs (imidacloprid + moxidectin)**

**Indications:** Advantage Multi for Dogs is indicated for the prevention of heartworm disease and the treatment of circulating microfilariae in heartworm-positive dogs. Advantage Multi for Dogs kills adult fleas and is indicated for the treatment of flea infestations. Advantage Multi for Dogs is indicated for the treatment and control of sarcoptic mange. Advantage Multi for Dogs is also indicated for the treatment and control of the following intestinal parasites: Hookworms, Roundworms, and Whipworm.

**Important Safety Information:** CAUTION: Federal (U.S.A) law restricts this drug to use by or on the order of a licensed veterinarian. WARNING: DO NOT ADMINISTER THIS PRODUCT ORALLY. For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with the application site for two (2) hours following application. (See Contraindications, Warnings, Human Warnings and Adverse Reactions for more information).
Once-a-month topical solution for the prevention of heartworm disease, the treatment of circulating microfilariae, kills adult fleas, is indicated for the treatment of flea infestations, the treatment and control of sarcoptic mange, as well as the treatment and control of intestinal parasite infections in dogs and puppies that are at least 7 weeks of age and that weigh at least 3 lbs.

**WARNING:**
- DO NOT ADMINISTER THIS PRODUCT ORALLY.
- For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals.
- Children should not come in contact with application sites for two (2) hours after application.

(See Contraindications, Warnings, Human Warnings, and Adverse Reactions, for more information.)

**CAUTION:**
Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:**
Advantage Multi for Dogs (10% imidacloprid + 25% moxidectin) is a colorless to yellow ready-to-use solution packaged in single dose applicator tubes for topical treatment of dogs. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/kg (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin based on body weight. Imidacloprid is a chloronicotinyl nitrogen analogue insecticide. The chemical name for imidacloprid is 1-[(6-Chloro-3-pyridyl)methyl]-N-nitro-2-imidazolidinylidine. Moxidectin is a semisynthetic macrocyclic lactone endo-kclide derived from the actinomycete Streptomyces censepticus nonacyclicus. The chemical name for moxidectin is [6R, 23E, 25S, 3S]-5, 7, 9, 20, 20-pentamethyl-28-deoxy-25-(1, 3-dimethyl-1-butenyl)-6, 26-epoxy-23(-methoxyimino) milbemycin B.

**INDICATIONS:**
Advantage Multi for Dogs is indicated for the prevention of heartworm disease caused by Dirofilaria immitis and the treatment of Dirofilaria immitis circulating microfilariae in heartworm-positive dogs. Advantage Multi for Dogs kills adult fleas and is indicated for the treatment of flea infestations (Ctenocephalides felis). Advantage Multi for Dogs is indicated for the treatment and control of sarcoptic mange caused by Sarcoptes scabiei var. canis. Advantage Multi for Dogs is also indicated for the treatment and control of the following intestinal parasites:

<table>
<thead>
<tr>
<th>Intestinal Parasite</th>
<th>Adult</th>
<th>Immature Adult</th>
<th>Fourth Stage Larvae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworm Specias</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Uncinaria stenocephala</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Roundworm Species</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Toxocara canis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whipworm Species</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichuris vulpis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DOSEAGE AND ADMINISTRATION:**
The recommended minimum dose is 4.5 mg/kg (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin, once a month, by topical administration.

Do not apply to irritated skin.

1. Remove one dose applicator tube from the package. As specified in the following table, administer the entire contents of the Advantage Multi for Dogs tube that correctly corresponds with the body weight of the dog.

<table>
<thead>
<tr>
<th>Dog (lbs)</th>
<th>Advantage Multi For Dogs</th>
<th>Volume (mL)</th>
<th>Imidacloprid (mg)</th>
<th>Moxidectin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–9</td>
<td>Advantage Multi 9</td>
<td>0.4</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>9.1–20</td>
<td>Advantage Multi 20</td>
<td>1.0</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>20.1–55</td>
<td>Advantage Multi 55</td>
<td>2.5</td>
<td>250</td>
<td>62.5</td>
</tr>
<tr>
<td>55.1–88</td>
<td>Advantage Multi 88</td>
<td>4.0</td>
<td>400</td>
<td>100</td>
</tr>
<tr>
<td>88.1–110</td>
<td>Advantage Multi 110</td>
<td>5.0</td>
<td>500</td>
<td>125</td>
</tr>
</tbody>
</table>

* Dogs over 110 lbs. should be treated with the appropriate combination of Advantage Multi for Dogs tubes.

2. While holding the tube in an upright position, remove the cap from the tube.
3. Turn the cap over and press the other end of cap onto the tip of the tube.
4. Twist the cap to break the seal and then remove cap from the tube.

5. The dog should be standing for application. Part the hair on the back of the dog between the shoulder blades until the skin is visible. For dogs weighing 20 lbs or less, place the tip of the tube on the skin and apply the entire contents directly on the exposed skin at one spot between the shoulder blades. For dogs weighing more than 20 lbs, place the tip of the tube on the skin and apply the entire contents directly on the exposed skin at 3 or 4 spots on the top of the backline from the base of the neck to the upper back in an area inaccessible to licking. Do not apply an amount of solution at any one location that could run off the side of the dog.

Do not let this product get in your dog’s mouth or eyes. Do not allow the dog to lick any of the application sites for 30 minutes. In households with multiple pets, keep each treated dog separated from other treated dogs and other pets for 30 minutes after application to prevent licking the application sites.

(See WARNINGS.) Contact with eyes can lead to eye irritation and corneal ulceration. If contact with eyes occurs, hold the dog’s eyelids open, flush thoroughly with water, and contact your veterinarian.

Stiff hair, a damp appearance of the hair, pink skin, or a slight powdery described may be observed at the application site on some animals. This is temporary and does not affect the safety and effectiveness of the product.

Shampoing 90 minutes after treatment does not reduce the effectiveness of Advantage Multi for Dogs in the prevention of heartworm disease. Shampooing or water immersion 4 days after treatment will not reduce the effectiveness of Advantage Multi for Dogs in the treatment of flea infestations. However, shampooing as often as once weekly may reduce the effectiveness of the product against fleas.

**Heartworm Prevention:** For prevention of heartworm disease, Advantage Multi for Dogs should be administered at one-month intervals. Advantage Multi for Dogs may be administered year-round or at a minimum should start one month before the first expected exposure to mosquitoes and continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer Advantage Multi for Dogs immediately and resume the monthly dosing schedule. When replacing another heartworm preventative product in a heartworm prevention program, the first treatment with Advantage Multi for Dogs should be given within one month of the last dose of the former medication.

**Treatment of Circulating Microfilariae:** For the treatment of circulating D. immitis microfilaria in heartworm-positive dogs, Advantage Multi for Dogs should be administered at one-month intervals. Treatment with an approved adulticide therapy is recommended because Advantage Multi for Dogs is not effective for the treatment of adult D. immitis.

(See PRECAUTIONS.)

**Flea Treatment:** For the treatment of flea infestations, Advantage Multi for Dogs should be administered at one-month intervals. If the dog is already infested with fleas when the first dose of Advantage Multi for Dogs is administered, adult fleas on the dog will be killed.

However, reinfestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated. Dogs treated with imidacloprid, including those with pre-existing flea allergy dermatitis, have shown clinical improvement as a direct result of elimination of fleas from the dog.

**Treatment and Control of Intestinal Nematode Infections:** For the treatment and control of intestinal hookworm infections caused by Ancylostoma caninum and Uncinaria stenocephala (adults, immature adults and fourth stage larvae) and roundworm infections caused by Toxocara canis (adults and fourth stage larvae), and Toxascaris leonina (adults), and whipworm infections caused by Trichuris vulpis (adults), Advantage Multi for Dogs should be administered once as a single topical dose.

**Treatment and Control of Sarcoptic Mange:** For the treatment and control of sarcoptic mange caused by Sarcoptes scabiei var. canis, Advantage Multi for Dogs should be administered as a single topical dose. A second monthly dose may be administered if necessary.

**CONTRAINDICATIONS:**
Do not administer this product orally. (See WARNINGS.)
Do not use this product (containing 2.5% moxidectin) on cats.

**WARNINGS:**
For the first 30 minutes after application:
Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs, and
Separate treated dogs from one another and from other pets to reduce the risk of accidental ingestion.

Ingestion of this product by dogs may cause severe adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors.

In avermectin sensitive dogs, the signs may be more severe and may include coma and death.

* Some dogs are more sensitive to avermectin due to a mutation in the MDR1 gene. Dogs with this mutation may develop signs of severe avermectin toxicity if they ingest this product. The most common breeds associated with this mutation include Collies and Collie crosses.

* Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.
HUMAN WARNINGS:
Not for human use. Keep out of the reach of children.
Children should not be in contact with application sites for 2 (two) hours after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headaches; dizziness; and redness, burning, tingling, or numbness of the skin. Wash hands thoroughly with soap and warm water after handling.

If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidazolidinyl or methylparaben should avoid application of this product. In case of allergic reaction, contact a physician.

If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice.

The Safety Data Sheet (SDS) provides additional occupational safety information. For product questions, to report adverse reactions, or for a copy of the Safety Data Sheet (SDS), call Elanco Product & Veterinary Support at 888-545-5973.

PRECAUTIONS:
Do not dispense dose applicator tubes without complete safety and administration information.
Use with caution in sick, debilitated, or underweight animals. The safety of Advantix Multi for Dogs has not been established in breeding, pregnant, or lactating dogs. The safe use of Advantix Multi for Dogs has not been established in pregnant and/or lactating bitches. The use of Advantix Multi for Dogs is not effective against adult D. immitis. Although the number of circulating microfilariae is substantially reduced in most dogs following treatment with Advantix Multi for Dogs, the microfilaria count in some heartworm-positive dogs may increase or remain unchanged following treatment with Advantix Multi for Dogs alone or in a dosage regimen with melarsomine dihydrochloride.

(See ADVERSE REACTIONS and ANIMAL SAFETY – Safety Study in Heartworm-Positive Dogs.)

Advantix Multi for Dogs has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

ADVERSE REACTIONS:
Heartworm-Negative Dogs
Field Studies: Following treatment with Advantix Multi for Dogs or an active control, dog owners reported the following post-treatment reactions:

<table>
<thead>
<tr>
<th>Observation</th>
<th>Advantix Multi n = 128</th>
<th>Active Control n = 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>19 dogs (14.8%)</td>
<td>7 dogs (10.3%)</td>
</tr>
<tr>
<td>Residue</td>
<td>9 dogs (7.0%)</td>
<td>5 dogs (7.4%)</td>
</tr>
<tr>
<td>Medicinal Odor</td>
<td>5 dogs (3.9%)</td>
<td>None observed</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1 dog (0.8%)</td>
<td>1 dog (1.5%)</td>
</tr>
<tr>
<td>Inappetence</td>
<td>1 dog (0.8%)</td>
<td>1 dog (1.5%)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>1 dog (0.8%)</td>
<td>None observed</td>
</tr>
</tbody>
</table>

During a field study using 61 dogs with pre-existing flea allergy dermatitis, one (1.6%) dog localized pruritus immediately after imidacloprid application, and one investigator noted hyperesthesia at the application site of one dog (1.6%).

In a field safety and effectiveness study, Advantix Multi for Dogs was administered to 92 client-owned dogs with sarcoptic mange. The dogs ranged in age from 2 months to 12.5 years and ranged in weight from 3 to 231.5 pounds. Adverse reactions in dogs treated with Advantix Multi for Dogs included hematochezia, diarrhea, vomiting, lethargy, inappetence, and pyrexmia.

Laboratory Effectiveness Studies: One dog in a laboratory effectiveness study experienced weakness, depression, and unsteadiness between 6 and 9 days after application with Advantix Multi for Dogs. The signs resolved without intervention by day 10 post-application. The signs in this dog may have been related to peak serum levels of moxidectin, which vary between dogs, and occur between 1 and 21 days after application of Advantix Multi for Dogs.

The following clinical observations also occurred in laboratory effectiveness studies following application with Advantix Multi for Dogs and may be directly attributed to the drug or may be secondary to the intestinal parasites burden or other underlying conditions in the dogs: diarrhea, bloody stools, vomiting, anorexia, lethargy, coughing, ocular discharge, and nasal discharge. Observations at the application sites included drape, sniff or hair at the application site, and mild erythema, which resolved without treatment within 2 to 48 hours.

Heartworm-Positive Dogs
Field Study: A 58-day field safety study was conducted in 214 D. immitis heartworm and microfilaria positive dogs with Class 1, 2, or 3 heartworm disease. All dogs received Advantix Multi for Dogs on Study Days 0 and 28; 108 dogs also received melarsomine dihydrochloride on Study Days 1, 2, 14, and 15. All dogs were hospitalized for a minimum of 12 hours following each treatment. Effectiveness against circulating D. immitis microfilariae was >90% at five of six sites; however, one site had an effectiveness of 73.3%. The microfilaria count in some heartworm-positive dogs increased or remained unchanged following treatment with Advantix Multi for Dogs alone or in a dosage regimen with melarsomine dihydrochloride.

Following treatment with Advantix Multi for Dogs alone or in a dosage regimen with melarsomine dihydrochloride, the following adverse reactions were observed:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Dogs Treated with Advantix Multi for Dogs Only n = 106</th>
<th>Dogs Treated with Advantix Multi for Dogs + Melarsomine n = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>24 (22.6%)</td>
<td>23 (21.3%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>14 (13.2%)</td>
<td>42 (38.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (10.4%)</td>
<td>18 (16.7%)</td>
</tr>
<tr>
<td>Diarrhea, including hemorrhagic</td>
<td>10 (9.4%)</td>
<td>22 (20.4%)</td>
</tr>
<tr>
<td>Inappetence</td>
<td>7 (6.6%)</td>
<td>19 (17.6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (5.7%)</td>
<td>10 (9.3%)</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>1 (1%)</td>
<td>7 (6.5%)</td>
</tr>
</tbody>
</table>

Pulmonary
| Atelectasis       | 0                                                      | 1 (1%)                                                       |

Three dogs treated with Advantix Multi for Dogs in a dosage regimen with melarsomine dihydrochloride died of pulmonary embolism from death and dying heartworms. One dog, treated with Advantix Multi for Dogs and melarsomine dihydrochloride, experienced pulmonary hemorrhage and responded to supportive medical treatment. Following the first treatment with Advantix Multi for Dogs alone, two dogs experienced adverse reactions (coughing, vomiting, and dyspnea) that required hospitalisation. In both groups, there were no adverse reactions to Advantix Multi for Dogs following the first treatment versus the second treatment.

To report a suspected adverse reaction, call 888-545-5973.

Post-Approval Experience (2022)
The following adverse events are based on post-approval adverse drug experience reporting for Advantix Multi for Dogs. Not all adverse events are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product use. For more information, contact Elanco at 1-888-868-6476 or http://www.fda.gov/reportmala.

Serious reactions, including neurologic signs and death have been reported when cats have been exposed (orally and topically) to this product.

In humans, nausea, numbness or tingling of the mouth/throat, ocular and dermal irritation, pruritus, headache, vomiting, diarrhea, depression and dyspnea have been reported following exposure to this product.

Contact Information:
For product questions, to report adverse drug experiences, or for a copy of the Safety Data Sheet (SDS), call Elanco Product & Veterinary Support at 888-545-5973.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportmala.

ANIMAL SAFETY:
Heartworm-Negative Dogs
Field Study: In a controlled, double-masked, field safety study, Advantix Multi for Dogs was administered to 128 dogs of various breeds, 3 months to 15 years of age, weighing 4 to 157 pounds. Advantix Multi for Dogs was used safely in dogs concomitantly receiving ACE inhibitors, angiotensin receptor blockers, angiotensin II receptor blockers, corticosteroids, immunomodulators, anticonvulsants, antiviral agents, anticonvulsants, antiepileptics, antihistamines, and beta-blockers. In both groups, the controls, the surrogates, and the study dogs were found to be safe and effective at all doses.

(See ADVERSE REACTIONS.)

Safety Study in Puppies: Advantix Multi for Dogs was applied topically at 1, 3, and 5X the recommended dose 2 to 7-week-old Beagle puppies every 2 weeks for 6 treatments on study days 0, 1, 2, 3, 4, 5, and 6. Works, dosing, and dosing were observed in all groups, including the controls. The control treatment was seen in one puppy from the 1X treatment group (day 57), in two puppies from the 3X treatment group (days 1 and 79), and in one puppy from the 5X treatment group (day 1). Two puppies each in the 1X, 3X, and 5X groups had decreased appetite within 24 hours post-dosing. One puppy in the 5X treatment group had pruritus for one hour following the first treatment. One puppy from the 5X treatment group displayed rapid, difficult breathing from 4 to 8 hours following the second treatment.

Dermal Dose Tolerance Study: Advantix Multi for Dogs was administered topically to 8-month-old Beagle dogs at 10X the recommended dose of 2 dogs. One dog showed signs of treatment site irritation after application. Two dogs vomited, one at 5 hours and one at 6 days post-treatment. Increased RBC, hemoglobin, and packed cell volume were observed in all treated groups. Dogs treated in the treated group did not gain as much weight as the control group.

Oral Safety Study in Beagles: Advantix Multi for Dogs was administered orally at the recommended dose of 12 dogs. Six dogs vomited within 1 hour of receiving the test article, 2 of these dogs vomited again at 2 hours, and 1 dog vomited again up to 18 hours post-dosing. One dog exhibited diaphoresis (nervousness) 1 hour post-dosing. Another dog exhibited abnormal neurological signs (circling, ataxia, generalized muscle tremors, and dilated pupils with a slow pupillary light response) starting at 4 hours post-dosing through 18 hours post-dosing. Without treatment, this dog was neurologically normal at 24 hours and had a normal appetite by 48 hours post-dosing.

(See CONTRAINDICATIONS.)
Dermal Safety Study in Ivermectin-Sensitive Collies: Advantage Multi for Dogs was administered topically at 3 and 5X the recommended dose every 28 days for 3 treatments to Collies which had been prescreened for avermectin sensitivity. No clinical abnormalities were observed.

Oral Safety Study in Ivermectin-Sensitive Collies: Advantage Multi for Dogs was administered orally to 5 pre-screened Ivermectin-sensitive Collies. The Collies were asymptomatic after ingesting 10 % of the minimum labeled dose. At 40 % of the minimum recommended topical dose, 4 of the dogs experienced neurological signs indicative of avermectin toxicity including depression, ataxia, mydriasis, salivation, muscle fasciculation, and coma, and were euthanized.

(See CONTRAINDICATIONS.)

Heartworm-Positive Dogs
Laboratory Safety Study in Heartworm-Positive Dogs: Advantage Multi for Dogs was administered topically at 1 and 5X the recommended dose every 14 days for 3 treatments to dogs with adult heartworm infections and circulating microfilaria. At 5X, one dog was observed vomiting three hours after the second treatment. Hypersensitivity reactions were not seen in the 5X treatment group. Microfilaria counts decreased with treatment.

STORAGE INFORMATION:
Store at temperatures between 4 °C (39 °F) and 25 °C (77 °F), avoiding excess heat or cold.

HOW SUPPLIED:
Applications Per Package
6 x 0.4 mL tubes
6 x 1.0 mL tubes
6 x 2.5 mL tubes
6 x 4.0 mL tubes
6 x 5.0 mL tubes

Revised: January 2023
Approved by FDA under NADA #141-251
Made in Germany
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Manufactured for:
Elanco US Inc
Greenfield, IN 46140 U.S.A.
**Comfortis™ (spinosad)**

**Chewable Tablets**

**COMFORTIS®-Cats**

**spinosad**

**Chewable Tablets**

**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/kg (60 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-bacterial, non-toxic to mammals, fish, birds, and other non-target organisms.

**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 muscarinic acetylcholine receptors. The exact mechanism by which spinosad affects these receptors is not known. Prolonged spinosad-induced hyperexcitation 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.

**Effectiveness:** In a well-controlled laboratory study, COMFORTIS became effective within 30 minutes after administration and demonstrated 96% effectiveness within 4 hours. COMFORTIS killed fleas before they could lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 7. If a single 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 counts reduced by 97.5% were observed one month after the first treatment and 93.0% after three monthly treatments with COMFORTIS. Fleas with pre-existing signs of flea allergy dermatitis showed improvement in pruritus, ear, and anal gland. The long-term effects of phospholipidosis are unknown. The administration of COMFORTIS was not associated with any clinically significant changes in hematological, clinical chemistry, coagulation, or urinalysis parameters. Cats administered COMFORTIS once monthly for 6 months in the 3X and 5X dose groups demonstrated cytochemical vacuolation, consistent with phospholipidosis, in the liver, lung, and adrenal gland.

**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 and was seen with greater frequency in cats in the treated groups; it did not increase with increasing doses. Loosening of the maxillary incisors 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 in treated companion animals. Cats administered COMFORTIS once monthly for 6 months in the 3X and 5X dose groups demonstrated cytochemical 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 changes in gross necropsy or histopathological changes.

**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, and 560 mg. Each tablet size is available in color-coded packages of 6 tablets.

**COMFORTIS®-Dogs**

**spinosad**

**Chewable Tablets**

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

**Description:** COMFORTIS is available in five 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/kg (30 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-bacterial, non-toxic to mammals, fish, birds, and other non-target organisms.

**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 muscarinic acetylcholine receptors. The exact mechanism by which spinosad affects these receptors is not known. Prolonged spinosad-induced hyperexcitation 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.

**Effectiveness:** In a well-controlled laboratory study, COMFORTIS became effective within 30 minutes after administration and demonstrated 96% effectiveness within 4 hours. COMFORTIS killed fleas before they could lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 7. If a single 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 by 97.5% were observed one month after the first treatment and 93.0% after three monthly treatments with COMFORTIS. Cats with pre-existing signs of flea allergy dermatitis showed improvement in pruritus, ear, and anal gland. The long-term effects of phospholipidosis are unknown. The administration of COMFORTIS was not associated with any clinically significant changes in gross necropsy or histopathological changes.

**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 and was seen with greater frequency in cats in the treated groups; it did not increase with increasing doses. Loosening of the maxillary incisors 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 in treated companion animals. Cats administered COMFORTIS once monthly for 6 months in the 3X and 5X dose groups demonstrated cytochemical 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 changes in gross necropsy or histopathological changes.

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**Effectiveness:** In a well-controlled laboratory study, COMFORTIS became effective within 30 minutes after administration and demonstrated 96% effectiveness within 4 hours. COMFORTIS killed fleas before they could lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 7. If a single 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 by 97.5% were observed one month after the first treatment and 93.0% after three monthly treatments with COMFORTIS. Cats with pre-existing signs of flea allergy dermatitis showed improvement in pruritus, ear, and anal gland. The long-term effects of phospholipidosis are unknown. The administration of COMFORTIS was not associated with any clinically significant changes in gross necropsy or histopathological changes.

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**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 dogs: 140, 270, and 560 mg. Each tablet size is available in color-coded packages of 6 tablets.
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, wash out 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 the fleas 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 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.

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

Serious adverse reactions have been reported following concurrent 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 breeding females (see ANIMAL SAFETY). Use with caution in dogs with pre-existing epilepsy (see ADVERSE REACTIONS). The sale use of COMFORTIS in breeding males needs to be 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 on 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.

<table>
<thead>
<tr>
<th>Percentage of Dogs (%) with Adverse Reactions</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMFORTIS Chewable Tablets (n=139)</td>
<td>Active Control (n=140)</td>
<td>Active Control (n=125)</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>3.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Cough</td>
<td>3.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Polyuria</td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Incontinence</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Erythema</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Excessive Salivation</td>
<td>0.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* This number (n=139) is lower 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 the US and European field studies, no dogs experienced seizures when dosed with COMFORTIS at the therapeutic dose range of 13.5-27.3 mg/kg (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that reached higher than the maximum recommended dose of 27.3 mg/kg (60 mg/kg) experienced at least one seizure within the week 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 following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions listed in decreasing order of frequency: vomiting, depression/lethargy, anorexia, ataxia, seizures, salivation, tremors, hyperactivity, and convulsions.

Following concomitant extra-label use of ivermectin with COMFORTIS, 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 COMFORTIS when used concurrently with heartworm preventative according to label directions.

For technical assistance or to report suspected adverse drug events, contact Elianone US Inc. at 1-866-549-5873.

For additional information about adverse drug events reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalsts.

Mode of Action:
The primary target of action of COMFORTIS is insects is an activator of nicotinic acetylcholine receptors (nAChRs). Spinosad does not interact with known insecticidal binding sites of other nicotinic acetylcholine receptors; however, it activates nAChRs in insects, which results in muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosad-induced hyperexcitability results in prostration, paralysis, and death of fleas. 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 100% effectiveness within 4 hours. COMFORTIS kills 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 monthly treatments with COMFORTIS. 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.

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

In a dose tolerance study, COMFORTIS 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 3 days of treatment, usually within 0.5 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 was not associated with any clinically significant changes in hematology, clinical chemistry, urinalysis, or post-mortem parameters. Moderate increases in ALT occurred in all dogs treated with COMFORTIS. By day 28, ALT values had returned to near baseline levels. Phosphoribosylation (vacuolation) of the lymph node tissue was seen in all dogs treated with COMFORTIS, the long-term effects of which are unknown.

In a margin of safety study, COMFORTIS 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 controls. 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 12 weeks of age. None of the doses tested were not be used in pregnant and lactating females. Concentrations of nAChR were unknown.

Treatment with COMFORTIS was not associated with any other clinically significant adverse clinical observations, gross necropsy or histopathological changes.

In a reproductive safety study, COMFORTIS 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. In most cases, litter birth rates in the dose groups were similar to those in the control group.

Information for Cat and Dog Owners
COMFORTIS**-Cats (spinosad)
Chewable Tablets
Your veterinarian has chosen to prescribe COMFORTIS to meet your flea treatment and prevention needs. Controlling fleas is important to the health of your cat. Please read this leaflet, which describes the proper use of COMFORTIS to treat and prevent flea infestations. If you have any questions about this information, please consult your veterinarian. Additional information can be found at www.comfortis.com.

What is COMFORTIS?
COMFORTIS is a chewable, flavored tablet that you give to your cat to kill fleas and prevent flea infestations for one month. COMFORTIS is for monthly use in cats and kittens 14 weeks of age or older and 1.4 pounds of body weight or more.

Why has my veterinarian prescribed COMFORTIS?
Your veterinarian has provided this medication to either prevent a flea infestation or to treat an existing flea infestation on your cat.
What should I discuss with my veterinarian regarding COMFORTIS for my cat?

Your veterinarian is your cat’s healthcare expert and can make the best recommendation for medications for your cat. This includes the prevention and treatment of parasites such as fleas that may cause conditions that include flea allergy dermatitis, anemia, and other flea-related problems.

Key points of your discussion may include the following:

- Treatment with COMFORTIS may begin at any time of the year, preferably starting one month before fleas become active and continuing through the end of flea season.
- In households where fleas may be present, monthly treatment with COMFORTIS should continue the entire year without interruption.
- If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
- To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea protection product.
- COMFORTIS is not for use in humans. Like all medications, keep COMFORTIS out of reach of children.

How should I give COMFORTIS to my cat?

Give COMFORTIS with food for maximum effectiveness. COMFORTIS is a chewable tablet that can be consumed by cats when offered just prior to or just after feeding. Alternatively, COMFORTIS may be offered in food or administer like other tablet medications. Give COMFORTIS to your cat once a month. To help you remember the monthly dosing schedule, stick-on labels are included for your calendar.

What if I give more than the prescribed amount of COMFORTIS to my cat?

COMFORTIS has been tested in many types of cats, and no severe adverse reactions have been reported. At elevated doses, the most severe adverse reaction observed was increased vomiting and loose stool. In the event of possible overdose, contact your veterinarian, who is the healthcare expert for your cat.

Should I restrict either my cat’s activity or contact with my cat after the medication is consumed?

Since COMFORTIS is an oral formulation, you may maintain normal activities and interactions with your cat.

How quickly will COMFORTIS kill fleas?

In a laboratory study, COMFORTIS killed fleas within 30 minutes and killed 100% of the fleas within 24 hours. COMFORTIS kills fleas before they can lay eggs.

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

COMFORTIS 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 control product to help control the flea population. Female fleas that are living on animals produce eggs that fall from the animals into their surroundings. These eggs hatch within a week; larvae then emerge and spin cocoons to become pupae. The entire life cycle can be completed in as little as 3 weeks, with new adult fleas emerging from the pupae to jump onto your cat. Because each female flea can lay up to 50 eggs per day, there is potential for a large build-up of eggs, larvae, and pupae, resulting in a constant supply of new adults emerging in the cat’s environment.

Regardless of the product used to kill the fleas, the cat can continue to be exposed to the fleas that live in the environment. If these fleas jump onto the cat, they will be killed by COMFORTIS. If you see fleas on your cat within a month after your cat receives COMFORTIS, it is most likely that these are new fleas that have recently emerged from pupae and jumped onto the cat. These new fleas will be killed before they can produce eggs that contaminate the environment.

Is it safe to give my cat COMFORTIS?

COMFORTIS has been demonstrated to be safe in cats when used according to label directions. It is safe in kittens 14 weeks of age and older, in multiple laboratory studies and in a field study in household cats. The safe use of COMFORTIS in breeding, pregnant, or lactating cats has not been established.

What side effects might occur with COMFORTIS?

Like all medications, side effects may occur. In some cases, cats vomited after receiving COMFORTIS. If vomiting occurs within one hour of administration, refeed with another full dose. Additional adverse reactions observed in studies were lethargy, decreased appetite, weight loss, and diarrhea.

Can other medications be given while my cat is taking COMFORTIS?

Yes, other medications are given safely with a wide variety of products and medications. Your veterinarian should be made aware of all medications, including over-the-counter (OTC) medications, that you are giving to your cat. For heartworm prevention, use products that are specifically prescribed by your veterinarian.

How should COMFORTIS be stored?

Store at 39° to 77°F (20° to 25°C). Temporary periods of time outside of this range between 59° to 86°F (15° to 30°C) are permitted. If you have questions regarding the use of this product, consult your veterinarian, your cat’s healthcare expert. Additional information can be found at www.comfortis.com.

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 FDA at 1-888-FDA-VETS or www.fda.gov/animaldrugs.

COMFORTIS® Dogs (spinosad)

Chewable Tablets

Your veterinarian has chosen to prescribe COMFORTIS to treat your flea and tick infestation needs. Controlling fleas is very important to the health of your dog. Please read this leaflet, which describes the use of COMFORTIS to treat and prevent flea infestations. If you have any questions about this information, please consult your veterinarian. Additional information can be found at www.comfortis.com.

What is COMFORTIS?

COMFORTIS is a chewable, flavored tablet that you give to your dog to kill fleas and prevent flea infestations for one month. COMFORTIS is for monthly use in dogs and puppies 14 weeks of age or older and 5 pounds of body weight or greater.

Why has my veterinarian prescribed COMFORTIS?

Your veterinarian has provided this medication to your dog to prevent flea infestation or to treat an existing infestation on your dog.
From the study.

Lotilaner has the chemical composition of 5-[(3S,4S)-4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trfluoroacetyl)-3-isoxazolyl]-3-methyl-N-[2-oxo-2-(2,2,2-trifluoroethoxy)ethyl]-2-thiophencarboxamid.

**Indications:**
CREDELIO kills adult fleas and is indicated for the treatment and prevention of flea infestations (Ctenocephalides felis) and the treatment and control of tick infestations [Amblyomma americanum (lone star tick), Dermacentor variabilis (American dog tick), Ixodes scapularis (black-legged tick) and Rhipicephalus sanguineus (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

**Dosage and Administration:**
CREDELIO is given orally once a month, at the minimum dosage of 9 mg/lb (20 mg/kg).

**Dosage Schedule:**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Lotilaner Per Chewable Tablet (mg)</th>
<th>Chewable Tablets Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4 to 6.0 lbs</td>
<td>56.25</td>
<td>One</td>
</tr>
<tr>
<td>6.1 to 12.0 lbs</td>
<td>112.5</td>
<td>One</td>
</tr>
<tr>
<td>12.1 to 25.0 lbs</td>
<td>225</td>
<td>One</td>
</tr>
<tr>
<td>25.1 to 50.0 lbs</td>
<td>450</td>
<td>One</td>
</tr>
<tr>
<td>50.1 to 100.0 lbs</td>
<td>900</td>
<td>One</td>
</tr>
<tr>
<td>Over 100.0 lbs</td>
<td>Administer the appropriate combination of chewable tablets</td>
<td></td>
</tr>
</tbody>
</table>

CREDELIO must be administered with food (see Clinical Pharmacology).

Treatment with CREDELIO can begin at any time of the year and can continue year-round without interruption.

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

**Warnings:**
Not for human use. Keep this and all drugs out of the reach of children. Keep CREDELIO in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

**Precautions:**
Lotilaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders. The safe use of CREDELIO in breeding, pregnant or lactating dogs has not been evaluated.

**Adverse Reactions:**

In a well-controlled U.S. field study, which included 284 dogs (198 dogs treated with CREDELIO and 86 dogs treated with an oral active control), there were no serious adverse reactions. Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence of 1% or greater are presented in the following table.

### Dogs with Adverse Reactions in the Field Study

<table>
<thead>
<tr>
<th>Adverse Reaction (AR)</th>
<th>CREDELIO Group: Number (and Percent) of Dogs with the AR (n=198)</th>
<th>Active Control Group: Number (and Percent) of Dogs with the AR (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>3 (1.5%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Elevated Blood Urea Nitrogen (BUN)</td>
<td>2 (1.0%)*</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Polypuria</td>
<td>2 (1.0%)*</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1.0%)*</td>
<td>2 (2.3%)</td>
</tr>
</tbody>
</table>

*Two geriatric dogs developed mildly elevated BUN (34 to 54 mg/dL; reference range: 6 to 31 mg/dL) during the study. One of these dogs also developed polypuria and a mildly elevated potassium (6.5 mEq/L; reference range: 3.6 to 5.5 mEq/L) and phosphorous (6.4 mg/dL; reference range: 2.5 to 6.0 mg/dL). The other dog also developed a mildly elevated creatinine (1.7 to 2.0 mg/dL; reference range: 0.5 to 1.6 mg/dL) and weight loss.

In addition, one dog experienced intermittent head tremors within 1.5 hours of administration of vaccines, an ear cleaning performed by the owner, and its first dose of CREDELIO. The head tremors resolved within 24 hours without treatment. The owner elected to withdraw the dog from the study.

In an Australian field study, one dog with a history of seizures experienced seizure activity (tremors and glazed eyes) six days after receiving CREDELIO. The dog recovered without treatment and completed the study. In the U.S. field study, two dogs with a history of seizures received CREDELIO and experienced no seizures throughout the study.

In three well-controlled European field studies and one U.S. laboratory study, seven dogs experienced episodes of vomiting and four dogs experienced episodes of diarrhea between 6 hours and 3 days after receiving CREDELIO.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc. at 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/reportanimalads.

**Clinical Pharmacology:**

Following oral administration of 43 mg/kg (approximately 1X the maximum labeled dose), peak lotilaner concentrations were achieved between 6 hours and 3 days in dogs 2 months of age and between 1 and 7 days in dogs 10 months of age. Dogs 2 months of age had a shorter elimination half-life (average of 9.6 days) than at 10 months of age (average of 28.4 days). Due to reduced drug bioavailability in the fasted state, CREDELIO must be administered with a meal or within 30 minutes after feeding.

**Mode of Action:**
Lotilaner is an ecdysteroidic derivative belonging to the isoxazoline group. Lotilaner inhibits insect and acarine gamma-aminobutyric acid (GABA)-gated chloride channels. This inhibition blocks the transfer of chloride ions across cell membranes, which results in uncontrolled neuromuscular activity leading to death of insects and acarines. The selective toxicity of lotilaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines’ GABA receptors versus mammalian GABA receptors.

**Effectiveness:**
In well-controlled European laboratory studies, CREDELIO began to kill fleas four hours after administration or infestation, with greater than 99% of fleas killed within eight hours after administration or infestation for 35 days. In a well-controlled U.S. laboratory study, CREDELIO demonstrated 100% effectiveness against adult fleas 12 hours after administration or infestation for 35 days.

In a 90-day well-controlled U.S. field study conducted in households with existing flea infestations of varying severity, the effectiveness of CREDELIO against fleas on Days 30, 60 and 90 compared to baseline was 99.5%, 100% and 100%, respectively. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis and pruritus as a direct result of eliminating fleas.

In a well-controlled laboratory study, CREDELIO killed fleas before they could lay eggs, thus preventing subsequent flea infestations for 30 days after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, CREDELIO demonstrated > 97% effectiveness against Amblyomma americanum, Dermacentor variabilis, Ixodes scapularis and Rhipicephalus sanguineus ticks 48 hours after administration or infestation for 30 days. In a well-controlled European laboratory study, CREDELIO started killing Ixodes ricinus ticks within four hours after administration.

**Palatability:**
In the U.S. field study, which included 567 doses administered to 198 dogs, 80.4% of dogs voluntarily consumed CREDELIO when offered by hand or in an empty bowl, an additional 13.6% consumed CREDELIO when offered with food, and 6.0% required placement of the chewable tablet in the back of the dog’s mouth.

**Animal Safety:**

In a margin of safety study, CREDELIO was administered orally to 24 (8 dogs/group) 8-week-old Beagle puppies at doses of 43 mg/kg, 129 mg/kg, and 215 mg/kg (approximately 1, 3, and 5X the maximum labeled dose, respectively) every 28 days for eight consecutive doses. The 8 dogs in the control group (0X) were untreated. There were no clinically-relevant, treatment-related effects on clinical observations, physical and neurological examinations, body weights, food consumption, electrocardiograms, clinical pathology (hematology, clinical chemistries, coagulation profiles and urinalysis), gross pathology, histopathology, or organ weights.

Blood concentrations of lotilaner confirmed systemic exposure of all treated dogs, although the exposure was less than dose proportional at 5X.

In a well-controlled field study, CREDELIO was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics, steroids, NSAIDS, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of CREDELIO with other medications.

**Storage Information:**

Store at 15-25°C (59 -77°F), excursions permitted between 5 to 40°C (41 to 104°F).

**How Supplied:**
CREDELIO is available in five chewable tablet sizes for use in dogs: 56.25, 112.5, 225, 450, and 900 mg lotilaner. Each chewable tablet size is available in color-coded packages of 1, 3 or 6 chewable tablets.

Approved by FDA under NADA # 141-494

Manufactured for: Elanco US Inc
Greenfield, IN 46140 USA

Credelio W1a

PA102967X
INTERCEPTOR™
(milbemycin oxime)

INFORMATION FOR DOSING DOGS

The palatable once-a-month tablet that prevents heartworm disease, controls adult hookworm, and removes and controls adult roundworm and whipworm infections in dogs and puppies.

**Caution:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Keep this and all drugs out of the reach of children.

**Description:** INTERCEPTOR is available in four tablet sizes in color-coded packages for oral administration to dogs and puppies. Each tablet is formulated to provide a minimum of 0.23 mg/lb (0.5 mg/kg) body weight of milbemycin oxime. Milbemycin oxime consists of the oxime derivatives of 5-didehydromilbemycin in the ratio of approximately 80% A4 (C17H20NO7, MW 555.71) and 20% A2 (C16H18NO7, MW 541.68).

**Package color**

<table>
<thead>
<tr>
<th>Package color</th>
<th>Milbemycin oxime tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>2.3 mg*</td>
</tr>
<tr>
<td>Green</td>
<td>5.75 mg</td>
</tr>
<tr>
<td>Yellow</td>
<td>11.5 mg</td>
</tr>
<tr>
<td>White</td>
<td>23.0 mg</td>
</tr>
</tbody>
</table>

*for dogs only

**Indications:** INTERCEPTOR is indicated for use in the prevention of heartworm disease caused by *Dirofilaria immitis*, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworms) and *Trichuris vulpis* (whipworm) infections in dogs and in puppies four weeks of age or greater and two pounds body weight or greater.

**Dosage:** INTERCEPTOR is given orally, once a month, at the recommended minimum dosage rate of 0.23 mg milbemycin oxime per pound of body weight (0.5 mg/kg).

**Recommended Dosage Schedule for Dogs**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>INTERCEPTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10 lbs.</td>
<td>One tablet (2.3 mg)</td>
</tr>
<tr>
<td>11-25 lbs.</td>
<td>One tablet (5.75 mg)</td>
</tr>
<tr>
<td>26-50 lbs.</td>
<td>One tablet (11.5 mg)</td>
</tr>
<tr>
<td>51-100 lbs.</td>
<td>One tablet (23.0 mg)</td>
</tr>
</tbody>
</table>

Dogs over 100 lbs. are provided the appropriate combination of tablets.

**Administration:** INTERCEPTOR is palatable and most dogs will consume the tablet willingly when offered by the owner. As an alternative, the dual-purpose tablet may be offered in food or administered as other tablet medications. Watch the dog closely following dosing to be sure the entire dose has been consumed. If it is not entirely consumed, redose once with the full recommended dose as soon as possible.

INTERCEPTOR must be administered monthly, preferably on the same date each month. The first dose should be administered within one month of the dog’s first exposure to mosquitoes and monthly thereafter until the end of the mosquito season. If a dose is missed and a 30-day interval between dosing is exceeded, administer INTERCEPTOR immediately and resume the monthly dosing schedule.

If INTERCEPTOR replaces diethylcarbamazine (DEC) for heartworm prevention, the first dose must be administered as other tablet medications.

**Palatability:** Palatability trials conducted in 244 dogs from 10 different U.S. veterinary practices demonstrated that INTERCEPTOR is palatable and will be accepted by the owner by over 95% of dogs. The trial was comprised of dogs representing 60 different breeds and both sexes, with weights ranging from 2.1 lbs. to 143.3 lbs., and ages ranging from 8 weeks to 15 years.

**Precautions:** Do not use in puppies less than four weeks of age or less than two pounds of body weight. Prior to initiation of the INTERCEPTOR treatment program, dogs should be tested for existing heartworm infections. Infected dogs should be treated to remove adult heartworms and microfilariae prior to initiating treatment with INTERCEPTOR. Mild, transient hypersensitivity reactions manifested as labored respiration, vomiting, salivation and lethargy, have been noted in some treated dogs carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

**Adverse Reactions:** The following adverse reactions have been reported following the use of INTERCEPTOR: Depression/lethargy, vomiting, ataxia, anorexia, diarrhea, convulsions, weakness and hypersalivation.

**Efficacy:** INTERCEPTOR eliminates the tissue stage of heartworm larva and the adult stage of hookworm (*Ancylostoma caninum*), roundworms (*Toxocara canis*, *Toxascaris leonina*) and whipworm (*Trichuris vulpis*) infections when administered orally according to the recommended dosage schedule.

**Safety:** Milbemycin oxime has been tested safely in over 75 different breeds of dogs, including collies, pregnant females, breeding males and females, and puppies over two weeks of age.

In well-controlled clinical field studies, 786 dogs completed treatment with milbemycin oxime. Milbemycin oxime was used safely in animals receiving frequently used veterinary products such as vaccines, anthelminthics, antibiotics, steroids, flea collars, champics and dips.

Two studies in heartworm-infected dogs were conducted which demonstrated mild, transient hypersensitivity reactions in treated dogs with high microfilaria counts (see Precautions for reactions observed). Safety studies in pregnant dogs demonstrated that high doses (1.5 mg/kg *3X*) administered to pregnant females were given in an exaggerated dosing regimen (daily from mating through weaning) resulted in measurable concentrations of the drug in milk. Puppies nursing these females which received exaggerated dosing regimens demonstrated milbemycin-related effects. These effects were directly attributable to the exaggerated experimental dosing regimen. The product is normally intended for once-a-month administration only. Subsequent studies included using 3X daily from mating to one week before weaning and demonstrated no effects on the pregnant females or their litters. A second study where pregnant females were dosed once at 3X the monthly use rate either before, on the day of or shortly after whelping resulted in no effects on the puppies.

Some nursing puppies, at 2, 4, and 6 weeks of age, given greatly exaggerated oral milbemycin oxime doses (9.6 mg/kg = 19X) exhibited signs typified by tremors, vocalization and ataxia. These effects were all transient and puppies returned to normal within 24 to 48 hours. No effects were observed in puppies given the recommended dose of milbemycin oxime (0.5 mg/kg). This product has not been tested in dogs less than 1 kg weight.

A rising-dose safety study conducted in rough-coated collies, manifested a clinical reaction consisting of ataxia, pyrexia and periodic recumbency, in one of fourteen dogs treated with milbemycin oxime at 12.5 mg/kg (25X monthly use rate). Prior to receiving the 12.5 mg/kg dose (20X monthly use rate) on day 56 of the study, all animals had undergone an exaggerated dosing regimen consisting of 2.5 mg/kg milbemycin oxime (5X monthly use rate) on day 0, followed by 5.0 mg/kg (10X monthly use rate) on day 14 and 10.0 mg/kg (20X monthly use rate) on day 32. No adverse reactions were observed in any of the collies treated with this regimen up through the 10.0 mg/kg (20X monthly use rate) dose.

INTERCEPTOR must be administered monthly, preferably on the same date each month. The first dose must be administered as other tablet medications.

**How supplied:** INTERCEPTOR is available in four tablet sizes (see Dosage section), formulated according to the weight of the dog. Each tablet size is available in color-coded packages of 6 or 12 tablets each, which are packaged 10 per display carton.

**Storage conditions:** INTERCEPTOR should be stored at room temperature, between 59° and 77°F (15-25°C).

INFORMATION FOR DOSING CATS

The palatable once-a-month tablet that prevents heartworm disease and removes adult roundworms and hookworms in cats and kittens.

**Caution:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Keep this and all drugs out of the reach of children.

**Description:** INTERCEPTOR for Cats is available in three tablet sizes in color-coded packages for oral administration to cats and kittens. Each tablet is formulated to provide a minimum of 0.9 mg/lb (2.0 mg/kg) body weight of milbemycin oxime. Milbemycin oxime consists of the oxime derivatives of 5-didehydromilbemycin in the ratio of approximately 80% A4 (C17H20NO7, MW 555.71) and 20% A2 (C16H18NO7, MW 541.68).

**Indications:** INTERCEPTOR for Cats is indicated for use in the prevention of heartworm disease caused by *Dirofilaria immitis* and the removal of adult *Ancylostoma tubaeforme* (hookworm) and *Toxocara cati* (roundworm) in cats and kittens six weeks of age or greater and 1.5 lbs. body weight or greater.

**Dosage:** INTERCEPTOR for Cats is given orally, once a month, at the recommended minimum dosage rate of 0.9 mg milbemycin oxime per pound of body weight (2.0 mg/kg).

**Recommended Dosage Schedule for Cats**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>INTERCEPTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 to 6 lbs.</td>
<td>One tablet (5.75 mg)</td>
</tr>
<tr>
<td>6.1-12 lbs.</td>
<td>One tablet (11.5 mg)</td>
</tr>
<tr>
<td>12.1-25 lbs.</td>
<td>One tablet (23.0 mg)</td>
</tr>
</tbody>
</table>

Cats over 25 lbs. are provided the appropriate combination of tablets.

**Administration:** INTERCEPTOR for Cats is palatable and may be offered by the owner as a treat. As an alternative, the tablet may be offered in food or administered as other tablet medications.

**Palatability:** Palatability trials conducted in 72 cats demonstrated that cats were successfully dosed with INTERCEPTOR for Cats by the owner when they either offered the tablet as a treat, placed it in the cat’s mouth or placed the tablet in the cat’s food in 72% of cases. About 16% of the cats were dosed manually and 13% of the cats were not successfully dosed according to the protocol.

**Precautions:** Do not use in kittens less than six weeks of age or less than 1.5 lbs. body weight. Safety in heartworm-positive cats has not been established. Safety in breeding, pregnant, and lactating queens and breeding toms has not been established.

**Efficacy:** INTERCEPTOR for Cats eliminates the tissue stage of heartworm larvae and hookworm (*Ancylostoma tubaeforme*) and roundworm (*Toxocara cati*) infections when administered orally according to the recommended dosage schedule.

**Safety:** Milbemycin oxime has been tested safely in over 8 different breeds of cats.

In well-controlled clinical field studies 141 cats completed treatment with milbemycin oxime. Milbemycin oxime was used safely in animals receiving frequently used veterinary products such as vaccines, anthelminthics, antibiotics, steroids, flea collars, champics and dips.

Safety: Milbemycin oxime has been tested safely in 8 different breeds of cats.

How supplied: INTERCEPTOR for Cats is available in three tablet sizes (see Dosage section), formulated according to the weight of the cat. Each tablet size is available in color-coded packages of 6 or 12 tablets each, which are packaged 10 per display carton.

**Storage conditions:** INTERCEPTOR for Cats should be stored at room temperature, between 59° and 77°F (15-25°C).

Manufactured for: Elanco US Inc., Greenfield, IN 46140, USA

Approved by FDA under NADA # 140-915.

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Revision date: February 2021
INTERCEPTOR PLUS (milbemycin oxime/praziquantel)

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

Description
INTERCEPTOR PLUS is available in four strengths in color-coded packages for oral administration to dogs and puppies according to their weight. Each chewable flavored tablet is formulated to provide a minimum of 0.23 mg/pound (0.5 mg/kg) of milbemycin oxime and 2.28 mg/pound (5 mg/kg) of praziquantel. Milbemycin oxime consists of oxime derivatives of 5-didehydromilbemycins in the ratio of approximately 80% A₄(C₂₆H₄₅NO₇, MW 555.71) and 20% A₃(C₂₅H₄₃NO₇, MW 541.68).

Praziquantel is an isoquinoline anthelmintic with the chemical name 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11-bis-hydroxy-4H-pyrazino [2,1-a]isoquinolin-4-one. It is classified as a macrocyclic anthelmintic.

Indications
INTERCEPTOR PLUS is indicated for the prevention of heartworm disease caused by Dirofilaria immitis, and for the treatment and control of adult roundworm (Toxocara canis, Toxascaris leonina, adult hookworm (Ancylostoma caninum), adult whipworm (Trichuris vulpis), and adult tapeworm (Taenia pisiformis, Echinococcus multilocularis, Echinococcus granulosus, and Dipylidium caninum) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

Dosage and Administration
INTERCEPTOR PLUS should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes (see EFFECTIVENESS).

EFFECTIVENESS

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Milbemycin Oxime per chewable</th>
<th>Praziquantel per chewable</th>
<th>Number of chewables</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 8 lbs.</td>
<td>2.3 mg</td>
<td>22.8 mg</td>
<td>One</td>
</tr>
<tr>
<td>8.1 to 25 lbs.</td>
<td>5.75 mg</td>
<td>57 mg</td>
<td>One</td>
</tr>
<tr>
<td>25.1 to 50 lbs.</td>
<td>11.5 mg</td>
<td>114 mg</td>
<td>One</td>
</tr>
<tr>
<td>50.1 to 100 lbs.</td>
<td>23 mg</td>
<td>228 mg</td>
<td>One</td>
</tr>
<tr>
<td>Over 100 lbs.</td>
<td>Administer the appropriate combination of chewables.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INTERCEPTOR PLUS may be offered to the dog by hand or added to a small amount of dog food. The chewables should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

Heartworm Prevention: INTERCEPTOR PLUS should be administered at monthly intervals beginning within 1 month of the dog’s first seasonal exposure to mosquitoes and continuing until at least 6 months after the dog’s last seasonal exposure (see EFFECTIVENESS). INTERCEPTOR PLUS may be administered year-round without interruption. When switching from another heartworm preventative product to INTERCEPTOR PLUS, the full dose of INTERCEPTOR PLUS should be given within a month of the last dose of the former product.

Intestinal Nematode and Cestode Treatment and Control:
Dosage of INTERCEPTOR PLUS should be administered at monthly intervals beginning within 1 month of the dog’s first seasonal exposure to mosquitoes and continuing until at least 6 months after the dog’s last seasonal exposure (see EFFECTIVENESS). INTERCEPTOR PLUS may be administered year-round without interruption. When switching from another heartworm preventative product to INTERCEPTOR PLUS, the full dose of INTERCEPTOR PLUS should be given within a month of the last dose of the former product.

Contraindications
There are no known contraindications to the use of INTERCEPTOR PLUS.

Adverse Reactions
The following adverse reactions have been reported in dogs after administration of milbemycin oxime or praziquantel: vomiting, diarrhea, depression/lethargy, ataxia, anorexia, convulsions, weakness, and salivation.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US, Inc. at 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/reportanimalae.

Information for Owner or Person Treating Animal:
Echinococcus multilocularis and Echinococcus granulosus are tapeworms found in wild canids and domestic dogs. E. multilocularis and E. granulosus can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where E. multilocularis or E. granulosus are endemic should be instructed on how to minimize their risk of exposure to these tapeworms, as well as their dog’s risk of exposure. Although INTERCEPTOR PLUS (milbemycin oxime/praziquantel) was 100% effective in laboratory studies in dogs against E. multilocularis and E. granulosus, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans.

Because the prepatent period for E. multilocularis may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Effectiveness

Heartworm Prevention:
In a well-controlled laboratory study, INTERCEPTOR PLUS was 100% effective against induced heartworm infections when administered once monthly for 6 consecutive months. In well-controlled laboratory studies, neither one dose nor two consecutive doses of INTERCEPTOR PLUS provided 100% effectiveness against induced heartworm infections.

Intestinal Nematodes and Cestodes Treatment and Control:
Elimination of the adult stage of hookworm (Ancylostoma caninum), roundworm (Toxocara canis, Toxascaris leonina, whipworm (Trichuris vulpis) and tapeworm (Echinococcus multilocularis, Echinococcus granulosus, Taenia pisiformis and Dipylidium caninum) infections in dogs was demonstrated in well-controlled laboratory studies.

Palatability
In a field study of 115 dogs offered INTERCEPTOR PLUS, 108 dogs (94.0%) accepted the product when offered from the hand as if a treat, 1 dog (0.9%) accepted it from the bowl with food, 2 dogs (1.7%) accepted it when it was placed in the dog’s mouth, and 4 dogs (3.5%) refused it.

Animal Intervention
INTERCEPTOR PLUS:
In a repeated dose safety study, 40 ten-week-old puppies (10 per group) were dosed with either a sham dose (OX) or 1, 3, or 5X the maximum label exposure of INTERCEPTOR PLUS every 14 days for a total of seven treatments. Ataxia, lethargy, and salvation were seen in the 3X and 5X treated dogs following each of the seven doses. Vomiting was seen in all treatment groups but had a higher incidence in the 3X and 5X treatment groups.

In a repeated dose safety study, 64 six-week-old puppies (16 per group) were dosed with either a sham dose (OX) or 1, 3, or 5X the maximum label exposure of INTERCEPTOR PLUS every 14 days for a total of four treatments. Lethargy was observed in all groups. Ataxia was observed in the three treated groups, including one dog in the 1X treated group.

For both lethargy and ataxia the incidence and duration increased in the 3X and 5X groups. These signs were observed during the first 24 hours following treatment. Salivation and tremors were observed in the 3X and 5X treated dogs beginning immediately after dosing and up to six hours post-dosing. Vomiting was only observed in the 5X treatment group on most, but not all, treatment days.

For INTERCEPTOR PLUS the maximum exposure based on product dosing is 2.5 mg/kg for milbemycin oxime and 25.1 mg/kg for praziquantel, which is higher than the minimum effective dose used in the safety studies for milbemycin oxime (see below).

Milbemycin Oxime:
Two studies were conducted in heartworm-infected dogs treated with milbemycin oxime. Mild, transient hypersensitivity reactions were observed in dogs with high microfilaremae counts (see PRECAUTIONS).

Safety studies in pregnant dogs demonstrated that doses of 0.6X the maximum exposure dose of INTERCEPTOR PLUS (1.5 mg/kg of milbemycin oxime), administered daily from mating through weaning, resulted in measurable concentrations of milbemycin oxime in milk. Puppies nursing these females demonstrated milbemycin oxime-related effects (depression, decreased activity, diarrhea, dehydration, nasal discharge). A subsequent study, which evaluated the daily administration of 0.6X the maximum exposure dose of INTERCEPTOR PLUS, from mating until one week post-weaning, demonstrated no effects on the pregnant females or their litters. A study in which pregnant females were dosed once, at 0.6X the maximum exposure dose of INTERCEPTOR PLUS before, on the day of, or shortly after whelping, resulted in no effects on the puppies. Some nursing puppies, at 2, 4, and 6 weeks of age, administered oral doses of 9.6 mg/kg milbemycin oxime (3.8X the maximum exposure dose of INTERCEPTOR PLUS) exhibited tremors, vocalization, and ataxia. These effects were all transient and puppies returned to normal within 24 to 48 hours. No effects were observed in puppies administered 0.5 mg/kg milbemycin oxime (minimum label dose).

A rising-dose safety study conducted in rough-coated Collies resulted in ataxia, pyrexia, and periodic recumbency in one of fourteen dogs administered milbemycin oxime at 12.5 mg/kg (OX) the maximum exposure dose of INTERCEPTOR PLUS. Prior to receiving the 12.5 mg/kg dose on day 56 of the study, all animals had undergone a dosing regimen consisting of 2.5 mg/kg milbemycin oxime on day 0, followed by 5.0 mg/kg on day 14, and 10.0 mg/kg on day 32. No adverse reactions were observed in any of the Collies treated with doses less than 12.5 mg/kg.

Storage Information
Store at room temperature, between 59° and 77°F (15-25°C).

How Supplied
INTERCEPTOR PLUS is available in four strengths, formulated according to the weight of the dog. Each strength is available in color-coded packages of one, six or twelve chewable tablets each. Manufactured for: Elanco US Inc. Greenwood, IN 46140, USA. Approved by FDA under NADA # 141-338. Elanco, Elanco and the diagonal bar logo are trademarks of Elanco or its affiliates. © 2021 Elanco or its affiliates. Revision date: November 2020.
**Trifexis** (spinosad + milbemycin oxime)

**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 weight. Each chewable flavored tablet is formulated to provide a minimum spinosad and milbemycin oxime dose of 0.2 mg/kg (0.5 mg/kg). Spinosad is a member of the spinosyn class of insecticides, which are non-antibacterial tetramic acid macrolides. Spinosyn contains two major factors, spinosyn A and spinosyn D, derived from the naturally occurring bacterium, Saccharopolyspora spinosior.

**Trifexis** A and spinosyn D have the chemical compositions C_{13}H_{9}NO_3 and C_{13}H_{9}NO_3 respectively. Milbemycin oxime is a macrocyclic lactone antibiotic containing two major factors, A_2 and B_1 of milbemycin oxime. The approximate ratio of A_2 to B_1 is 20:8. Milbemycin A_2, spinosyn A has the chemical composition of C_{13}H_{9}NO_3 and milbemycin B_1, spinosyn A has the chemical composition of C_{13}H_{9}NO_3.

**Indications:** TRIFEXIS is indicated for the prevention of heartworm disease (Dirofilaria immitis), TRIFEXIS kills fleas and is indicated for the prevention and treatment of flea infestations (Ctenocephalides felis), and the treatment and control of adult hookworm (Ankylostoma caninum), adult roundworm (Toxocara canis and Toxascaris leonina) and adult whipworm (Trichuris vulpis) infections in dogs and puppies 5 weeks of age or older and 5 pounds of body weight or greater.

**Dosage and Administration:** TRIFEXIS given orally, once a month at the minimum dosage of 13.5 mg/kg (50 mg/kg) spinosad and 0.2 mg/kg (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).

**Dosage Schedule:**

<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>40</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 90 lbs</td>
<td>1,160</td>
<td>16</td>
<td>One</td>
</tr>
</tbody>
</table>

**EFFECTIVENESS:**

Administer TRIFEXIS with food for maximum effectiveness. To ensure heartworm prevention, owners should observe the dog for one hour after dosing. If vomitting occurs within an hour of administration, adminster 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 heartworm development or adult heartworm infections and flea infestations.

**Precautions:** 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.

**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, hookworms and whipworms 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 concurrent extra-label use of vermicated spinosad, 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 anthelminthic to remove adult heartworms before treating with TRIFEXIS. TRIFEXIS is ineffective against adult D. immitis. While the number of circulating microfilariae may decrease following treatment, TRIFEXIS is not indicated for microfilaria clearance (see ANIMAL SAFETY).

Mild, transient hypersensitivity reactions manifested as localized erythema, urticaria, 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 and 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 189-day study period, all observations of potential adverse reactions were recorded. Reactions occurred at an incidence of <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.

In an additional 167 dogs, vomiting, diarrhea, lethargy, and pruritus were reported in a single mild to severe 2% of the cases. The following table shows the percentage of dogs with adverse reactions by drug combination.

<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>1.28</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 US and European field studies, no clinically overt adverse events were recorded. The following adverse events were reported in the US study:

- One dog developed dermatitis.
- One dog developed pruritus.
- One dog developed lethargy.

In the European study:

- One dog developed dermatitis.
- One dog developed pruritus.
- One dog developed lethargy.

In both studies, the adverse events observed in the US study were not considered to be related to the treatment of TRIFEXIS.

**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.

**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 6-week-old Beagle puppies at doses of 1, 3, and 5 times the upper half of the pharmacodynamic dose range, every 28 days for 8 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 vomiting.

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 lipidosis observed microscopically.

The clinical relevance of this finding is unknown.

Plasma spinosad A, spinosad D, milbemycin A_2, and milbemycin B_1 concentrations were determined in the course of the study. At each dosing period, plasma spinosad A and spinosad D concentrations were greater than proportional across the dose range 1 to 5X.
Plasma melibiosin A, 5-cis-cones appeared to be dose proportional across range 1 to 5X by the end of the study.

Plasma concentrations of spinosad and melibioscin oxime indicate that systemic exposure was achieved throughout the study.

In an allometric-sensitive Collie used 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; 28 days and 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 important results 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. Pups with normal fetal heart sounds on fetal ultrasonographic examinations were evaluated for reproductive safety profiles. Litter size, body weight, pup survival, and the proportion of pups with malformations were comparable between treated and control groups. Pups from the 1X group included a pup with anophthalmia, a pup with a cleft palate and a pup with a cleft lip with anophthalmia. No malformations were observed in the 3X group. The 5X group had one pup with a cleft palate and a pup with a cleft lip with anophthalmia. No malformations were observed in the treatment groups. Pups born in the treatment groups and controls were observed for 30 days. Blood samples were collected from pups in the treatment group and controls. All pups were observed for up to 10 weeks. All pups were 100% treated for heartworm disease.

No treatment-related adverse reactions or signs of avermectin toxocosis were noted for adult females.

In a lactation study, TRIFEXIS was administered orally to pregnant Beagle dogs at 1, 3, and 5 times the upper half of the maternal dose band every 28 days prior to mating, during gestation, and during a six-week lactation period. Pups with normal fetal heart sounds on fetal ultrasonographic examinations were evaluated for reproductive safety profiles. Litter size, body weight, pup survival, and the proportion of pups with malformations were comparable between treated and control groups. Pups from the 1X group included a pup with a cleft palate and a pup with a cleft lip with anophthalmia. No malformations were observed in the 3X group. The 5X group had one pup with a cleft palate and a pup with a cleft lip with anophthalmia. No malformations were observed in the treatment groups. Pups born in the treatment groups and controls were observed for up to 10 weeks. All pups were 100% treated for heartworm disease.

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