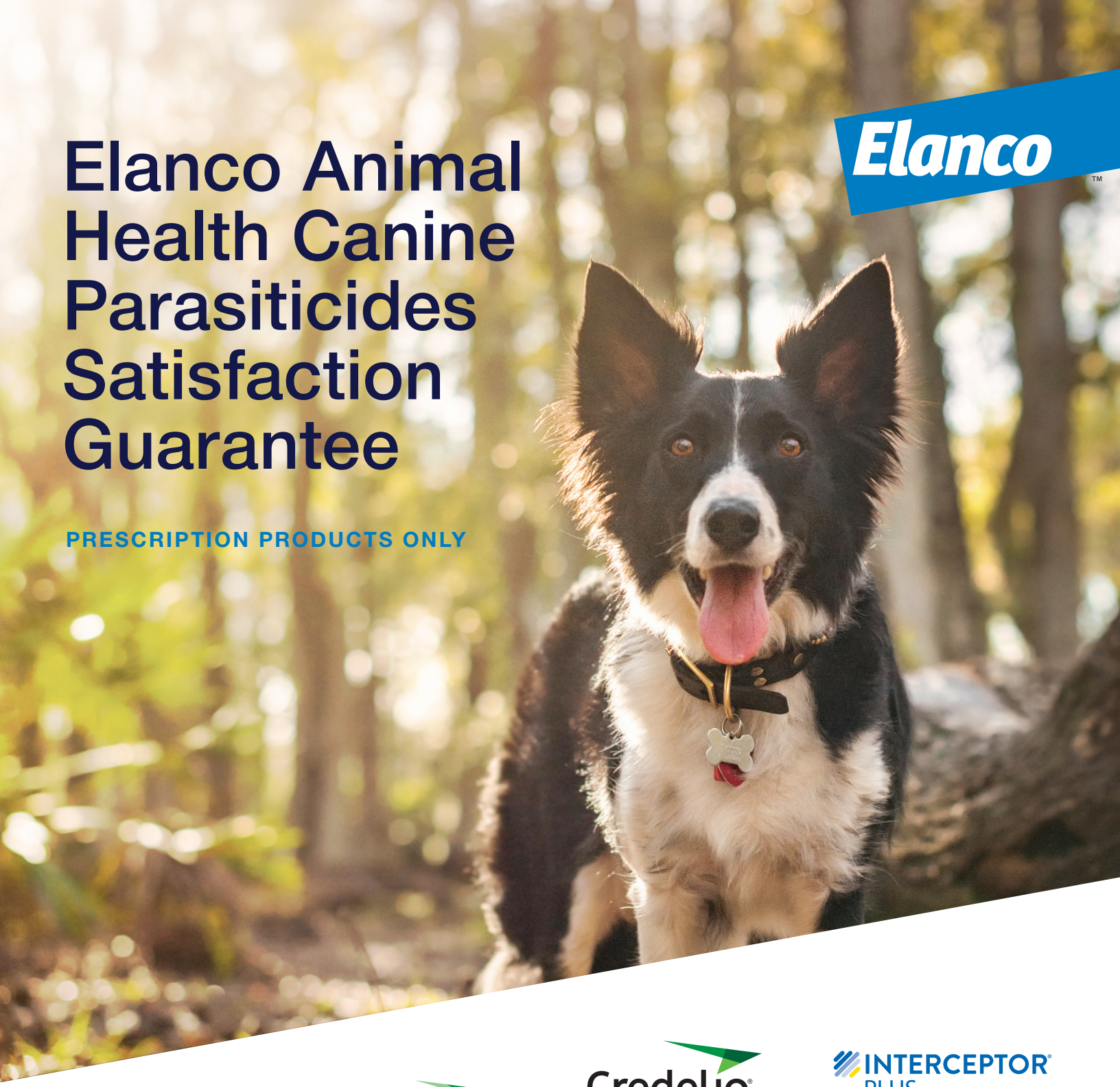

Elanco Animal Health Canine Parasiticides Satisfaction Guarantee

Elanco™

PRESCRIPTION PRODUCTS ONLY

Credelio Quattro™
(lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Credelio®
(lotilaner)

INTERCEPTOR® PLUS
(milbemycin oxime/praziquantel)

Trifexis®
(spinosad+milbemycin oxime)

advantage multi®
for dogs
(imidacloprid+moxidectin)

Comfortis™
(spinosad)

Interceptor®
(milbemycin oxime)

Advantage Multi for 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 Quattro, 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 Parasiticides 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 for 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.)

Elanco

Satisfaction Guarantee from the Brands You Trust

Credelio Quattro
(lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Delivers the broadest* parasite protection of its kind in a monthly chewable. Uses 4 powerful ingredients to protect against ticks, fleas, heartworms, tapeworms, roundworms, and hookworms (*Uncinaria stenocephala*). Safe for dogs and puppies 8 weeks and older, weighing 3.3 pounds or more.

Credelio
(lotilaner)

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
(spinosad+milbemycin oxime)

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.

advantage multi® for dogs
(imidacloprid+moxidectin)

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.

INTERCEPTOR PLUS
(milbemycin oxime/praziquantel)

Protects your dog against all 5 major worms. A once-monthly, tasty chew, flavored with real chicken prevents heartworm disease and protects against hookworms, roundworms, whipworms, and tapeworms. Safe for dogs and puppies 6 weeks or older and 2 pounds or more.

Comfortis™
(spinosad)

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
(milbemycin oxime)

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.

**Based on label comparison of the number of parasite types covered in an isoxazoline endectocide*

*** Data from two laboratory studies conducted in different locations using different cats and strains of fleas.*

Advantage Multi for 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.)

Heartworm Disease

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) | INTERCEPTOR PLUS (milbemycin oxime/praziquantel) | Trifexis (spinosad+milbemycin oxime) | advantage multi for dogs (imidadoprid+moxidectin) | Interceptor (milbemycin oxime)

Credelio Quattro, 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 immitus* 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 Credelio Quattro, 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 Credelio Quattro, Interceptor Plus, Trifexis, Interceptor*, or Advantage Multi for dogs
- If one or more doses is missed, a negative 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]

[1] *https://heartwormsociety.org/images/pdf/Canine-Guidelines-Summary.pdf. Accessed 11/06/2023.*
[2] *https://www.capcvet.org/guidelines/general-guidelines/. Accessed 11/06/2023.*

Hookworms, Roundworms, Whipworms, and Tapeworms

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) | INTERCEPTOR PLUS (milbemycin oxime/praziquantel) | Trifexis (spinosad+milbemycin oxime) | advantage multi for dogs (imidadoprid+moxidectin) | Interceptor (milbemycin oxime)

Credelio Quattro is indicated for the treatment and control of roundworm (immature adult and adult *Toxacara canis* and adult *Toxascaris leonina*), hookworm (adult *Uncinaria stenocephala*) and tapeworm (*Dipylidium caninum, Taenia pisiformis,* and *Echinococcus granulosus*) infections.

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 multilocularis, 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 and Credelio Quattro is not effective in treating and/or controlling whipworms 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 1 month prior to claim

** Applies in the use of dogs only.*

Advantage Multi for 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.)

Elanco

Fleas

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) | Credelio (lotilaner) | Trifexis (spinosad+milbemycin oxime) | advantage multi for dogs (imidacloprid+moxidectin) | Comfortis (spinosad)

Credelio Quattro, 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 Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) | Credelio (lotilaner)

Credelio Quattro and Credelio are 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 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 burgdoferi* 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 Quattro or Credelio[1] were used according to label directions
- Dog must test negative for *Borrelia burgdorferi* within 1 month of starting treatment with Credelio Quattro or Credelio[1] and have a negative test yearly thereafter
- Client must demonstrate that the dog received continuous protection with Credelio Quattro or Credelio[1] (purchase history may be required) from the date of the negative *Borrelia burgdorferi* test through the claim date

[1] *Credelio Quattro and Credelio are not labeled for the prevention of Lyme disease.*

Ticks *cont.*

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Credelio (lotilaner)

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 Quattro or Credelio[1] were used according to label directions
  - Client must demonstrate that the dog received continuous protection with Credelio Quattro or Credelio[1] (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 Quattro or Credelio[1] and positive confirmatory test indicating exposure to Lyme and *Borrelia burgdorferi*
  - Dog was vaccinated with an Elanco TruCan Lyme vaccine within the last 15 months

[1] Credelio Quattro and Credelio are not labeled for the prevention of Lyme disease.

Palatability

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Credelio (lotilaner)

COMPENSATION

- In the event a dog does not accept the tablet, Elanco will provide:
  - Product replacement to the veterinary hospital, or
  - A refund of the purchased product to the owner

ELIGIBILITY REQUIREMENTS

- Proof of prescription and purchase may be required

Skin Mites

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Credelio® (lotilaner)

COMPENSATION

- In the event a dog is diagnosed with skin mites, Elanco will reimburse the veterinary hospital for up to $250 in reasonable treatment costs

ELIGIBILITY REQUIREMENTS

- Product was used according to label directions for 2 consecutive months prior to diagnosis
- Diagnosis made via skin scrape or based on rule out of other dermatologic conditions including the exclusion of any identified secondary bacterial or other parasitic infections

Ear Mites

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Credelio® (lotilaner)

COMPENSATION

- In the event, a dog is diagnosed with ear mites, (*Otodectes cynotis*) Elanco will reimburse the veterinary hospital for up to $100 in reasonable treatment costs

ELIGIBILITY REQUIREMENTS

- Product was used according to label directions within 30 days of diagnosis

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)

Indication: 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® (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).

Credelio Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Indications: Credelio Quattro is indicated for the prevention of heartworm disease and the treatment and control of roundworm, hookworm* and tapeworm infections. Credelio Quattro kills adult fleas and is indicated for the treatment and prevention of flea infestations and the treatment and control of tick infestations for 1 month in dogs and puppies 8 weeks of age and older and weighing 3.3 pounds or greater.

Important Safety Information: Lotilaner, an ingredient in Credelio Quattro, belongs to the isoxazoline class and has been associated with neurologic adverse reactions like tremors, ataxia, and seizures even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders. Dogs should be tested for existing heartworm infections before Credelio Quattro administration as it is not effective against adult *D. immitis*. The safe use in breeding, pregnant, or lactating dogs has not been evaluated. The most frequently reported adverse reactions in clinical trials were vomiting and diarrhea. For complete safety information, please see Credelio Quattro product label or ask your veterinarian.

**Uncinaria stenocephala*

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Elanco

Elanco™

advantage multi™ for dogs

(imidacloprid+moxidectin)
Topical Solution

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 + 2.5 % 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/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin based on body weight.

Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name for imidacloprid is 1-[(6-Chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine. Moxidectin is a semisynthetic macrocyclic lactone endectocide derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus*. The chemical name for moxidectin is [6R, 23E, 25S(E)]-5-O- Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-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:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma caninum*	X	X	X
	Uncinaria stenocephala	X	X	X
Roundworm Species	*Toxocara canis*	X		X
	Toxascaris leonina	X		
Whipworm	*Trichuris vulpis*	X		

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

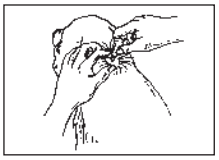
Do not apply to irritated skin.

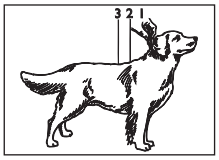
1. Remove one dose applicator tube from the package. As specified in the following table, administer the entire contents of the *Advantage Multi for Dogs* tube that correctly corresponds with the body weight of the dog.

Dog (lbs.)	Advantage Multi For Dogs	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
3–9	*Advantage Multi 9*	0.4	40	10
9.1–20	*Advantage Multi 20*	1.0	100	25
20.1–55	*Advantage Multi 55*	2.5	250	62.5
55.1–88	*Advantage Multi 88*	4.0	400	100
88.1–110*	*Advantage Multi 110*	5.0	500	125

* 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 push 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 residue may be observed at the application site on some animals. This is temporary and does not affect the safety and effectiveness of the product.

Shampooing 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 should 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 Microfilaria: 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 serious adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors.
In avermectin sensitive dogs,[a] the signs may be more severe and may include coma and death.[b]

[a] Some dogs are more sensitive to avermectins 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.

[b] 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 come in contact with application sites for two (2) 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 headache; 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, imidacloprid or moxidectin should administer the product with caution. 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 *Advantage Multi for Dogs* has not been established in breeding, pregnant, or lactating dogs. The safe use of *Advantage Multi for Dogs* has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight.

Prior to administration of *Advantage Multi for Dogs*, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of *Advantage Multi for Dogs* has not been evaluated when administered on the same day as an adulticide. *Advantage 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 *Advantage Multi for Dogs*, the microfilaria count in some heartworm-positive dogs may increase or remain unchanged following treatment with *Advantage Multi for Dogs* alone or in a dosing regimen with melarsomine dihydrochloride.
(See ADVERSE REACTIONS and ANIMAL SAFETY – Safety Study in Heartworm-Positive Dogs.)

Advantage 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 *Advantage Multi for Dogs* or an active control, dog owners reported the following post-treatment reactions:

OBSERVATION	Advantage Multi n = 128	Active Control n = 68
Pruritus	19 dogs (14.8%)	7 dogs (10.3%)
Residue	9 dogs (7.0%)	5 dogs (7.4%)
Medicinal Odor	5 dogs (3.9%)	None observed
Lethargy	1 dog (0.8%)	1 dog (1.5%)
Inappetence	1 dog (0.8%)	1 dog (1.5%)
Hyperactivity	1 dog (0.8%)	None observed

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

In a field safety and effectiveness study, *Advantage 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 *Advantage Multi for Dogs* included hematochezia, diarrhea, vomiting, lethargy, inappetence, and pyoderma.

Laboratory Effectiveness Studies: One dog in a laboratory effectiveness study experienced weakness, depression, and unsteadiness between 6 and 9 days after application with *Advantage 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 *Advantage Multi for Dogs*.

The following clinical observations also occurred in laboratory effectiveness studies following application with *Advantage Multi for Dogs* and may be directly attributed to the drug or may be secondary to the intestinal parasite 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 damp, stiff or greasy hair, the appearance of a white deposit on the hair, and mild erythema, which resolved without treatment within 2 to 48 hours.

Heartworm-Positive Dogs

Field Study: A 56-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 *Advantage Multi for Dogs* on Study Days 0 and 28; 108 dogs also received melarsomine dihydrochloride on Study Days – 14, 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 *Advantage Multi for Dogs* alone or in a dosing regimen with melarsomine dihydrochloride.

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

Adverse Reaction	Dogs Treated with Advantage Multi for Dogs Only n = 106	Dogs Treated with Advantage Multi for Dogs + Melarsomine n = 108
Cough	24 (22.6%)	25 (23.1%)
Lethargy	14 (13.2%)	42 (38.9%)
Vomiting	11 (10.4%)	18 (16.7%)
Diarrhea, including hemorrhagic	10 (9.4%)	22 (20.4%)
Inappetence	7 (6.6%)	19 (17.6%)
Dyspnea	6 (5.7%)	10 (9.3%)
Tachypnea	1 (< 1%)	7 (6.5%)
Pulmonary Hemorrhage	0	1 (< 1%)
Death	0	3 (2.8%)

Three dogs treated with *Advantage Multi for Dogs* in a dosing regimen with melarsomine dihydrochloride died of pulmonary embolism from dead and dying heartworms. One dog, treated with *Advantage Multi for Dogs* and melarsomine dihydrochloride, experienced pulmonary hemorrhage and responded to supportive medical treatment. Following the first treatment with *Advantage Multi for Dogs* alone, two dogs experienced adverse reactions (coughing, vomiting, and dyspnea) that required hospitalization. In both groups, there were more adverse reactions to *Advantage Multi for Dogs* following the first treatment than 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 *Advantage 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 exposure using this data.

The following adverse events reported in dogs are listed in decreasing order of reporting frequency: depression/lethargy, pruritus, vomiting, diarrhea, anorexia, application site reactions (alopecia, pruritus, erythema, and lesions, including blisters), hyperactivity, ataxia, trembling, seizures, panting, hypersalivation, anaphylaxis/anaphylactic reactions (hives, facial swelling, edema of the head), and corneal ulceration.

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/lips and 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/reportanimalae.

ANIMAL SAFETY:

Heartworm-Negative Dogs

Field Study: In a controlled, double-masked, field safety study, *Advantage Multi for Dogs* was administered to 128 dogs of various breeds, 3 months to 15 years of age, weighing 4 to 157 pounds. *Advantage Multi for Dogs* was used safely in dogs concomitantly receiving ACE inhibitors, anticonvulsants, antihistamines, antimicrobials, chondroprotectants, corticosteroids, immunotherapeutics, MAO inhibitors, NSAIDs, ophthalmic medications, sympathomimetics, synthetic estrogens, thyroid hormones, and urinary acidifiers. Owners reported the following signs in their dogs after application of *Advantage Multi for Dogs:* pruritus, flaky/greasy residue at the treatment site, medicinal odor, lethargy, inappetence, and hyperactivity.
(See ADVERSE REACTIONS.)

Safety Study in Puppies: *Advantage Multi for Dogs* was applied topically at 1, 3 and 5X the recommended dose to 7-week-old Beagle puppies once every 2 weeks for 6 treatments on days 0, 14, 28, 42, 56, and 70. Loose stools and diarrhea were observed in all groups, including the controls, throughout the study. Vomiting 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 appetites within 24 hours post-dosing. One puppy in the 1X treatment group had pruritus for one hour following the fifth treatment. A puppy from the 5X treatment group displayed rapid, difficult breathing from 4 to 8 hours following the second treatment.

Dermal Dose Tolerance Study: *Advantage Multi for Dogs* was administered topically to 8-month-old Beagle dogs at 10X the recommended dose once. One dog showed signs of treatment site irritation after application. Two dogs vomited, one at 6 hours and one at 6 days post-treatment. Increased RBC, hemoglobin, activated partial thromboplastin, and direct bilirubin were observed in the treated group. Dogs in the treated group did not gain as much weight as the control group.

Oral Safety Study in Beagles: *Advantage Multi for Dogs* was administered once orally at the recommended topical dose to 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 shaking (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/lb (50 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial tetracyclic macrolides. Spinosad contains two major factors, spinosyn A and spinosyn D, derived from the naturally occurring bacterium, *Saccharopolyspora spinosa*. Spinosyn A and spinosyn D have the chemical compositions 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione and 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione, respectively.

Indications:
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations *(Ctenocephalides felis)*, for one month, on cats and kittens 14 weeks of age and older and 4.1 pounds of body weight or greater.

Dosage and Administration:
COMFORTIS is given orally once a month, at the minimum dosage of 22.5 mg/lb (50 mg/kg).

Do not use the dosing schedule below when administering COMFORTIS to dogs, as it can result in an overdosage.

Dosage Schedule:

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
4.1 to 6 lbs	140	One
6.1 to 12 lbs	270	One
12.1 to 24* lbs	560	One

*Cats over 24 lbs should be administered the appropriate combination of tablets.

Administer COMFORTIS with food for maximum effectiveness.

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

If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.

Treatment with COMFORTIS may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of flea season. In areas where fleas are common year-round, monthly treatment with COMFORTIS should continue the entire year without interruption.

To minimize the likelihood of flea reinfestations, it is important to treat all animals within a household with an approved flea protection product.

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

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

Precautions:
Use with caution with concomitant extra-label use of ivermectin (see ADVERSE REACTIONS). The safe use of COMFORTIS in breeding, pregnant, or lactating cats has not been evaluated.

Adverse Reactions:
In a well-controlled US field study, which included a total of 211 cats (139 treated with COMFORTIS and 72 treated with an active topical control once a month for 3 treatments), no serious adverse reactions were attributed to the administration of COMFORTIS.

Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence > 1% within any of the 3 months of observations are presented in the following table. The most frequently reported adverse reaction in cats was vomiting.

Percentage of Cats (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS (n=139)	Active Topical Control (n=72)	COMFORTIS (n=135)	Active Topical Control (n=69)	COMFORTIS (n=132)	Active Topical Control (n=67)
Vomiting	14.4	1.4	14.8	1.4	13.6	4.5
Lethargy	3.6	0.0	0.7	0.0	1.5	1.5
Anorexia	2.2	0.0	0.7	0.0	2.3	1.5
Weight Loss	1.4	0.0	0.0	0.0	3.0	0.0
Diarrhea	1.4	1.4	0.7	2.9	2.3	1.5

Over the 3-month (3-dose) study, vomiting occurred on the day of or the day after at least one dose in 28.1% (39/139) of the cats treated with COMFORTIS and in 2.8% (2/72) of the cats treated with the active topical control. Three of the 139 cats treated with COMFORTIS vomited on the day of or the day after all three doses.

Two cats that received extra-label topical otic ivermectin on Day -1 of the field study developed lethargy on Day 1 after COMFORTIS administration on Day 0.

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

Mode of Action:
The primary target of action of COMFORTIS in insects is an activation of nicotinic acetylcholine receptors (nAChRs). Spinosad does not interact with known binding sites of other nicotinic or GABAergic insecticides such as neonicotinides, fiproles, milbemycins, avermectins, and cyclodienes. Insects treated with spinosad show involuntary muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosad-induced hyperexcitation results in prostration, paralysis, and flea death. The selective toxicity of spinosad between insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nAChRs.

Effectiveness:
In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 98% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 30.

If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment.

In a field study conducted in households with existing flea infestations, flea count reductions of 97.5% were observed one month after the first treatment and 99.3% after three monthly treatments with COMFORTIS. Cats with pre-existing signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis, and pruritus as a direct result of eliminating the fleas.

Animal Safety:
In a margin of safety study, COMFORTIS was administered orally to 14-week-old kittens at 1X, 3X, and 5X the upper half (75 – 100 mg/kg) of the therapeutic dose band for six monthly dosing intervals 28 days apart. Vomiting was observed across all groups, but was seen with greater frequency in cats in the treated groups; it did not increase with increasing doses. Loose stool was observed in all but the 3X treatment group. Food consumption was decreased in the 5X female cats. COMFORTIS was not associated with clinically significant changes in hematology, clinical chemistry, coagulation, or urinalysis parameters. Cats administered COMFORTIS once monthly for 6 months in the 3X and 5X dose groups demonstrated cytoplasmic vacuolation, consistent with phospholipidosis, in the liver, lung, and adrenal gland. The long term effects of phospholipidosis are unknown. The administration of COMFORTIS was not associated with any clinically significant, gross necropsy or histopathological changes.

In a well-controlled field study, COMFORTIS was administered safely in conjunction with other frequently used veterinary products, including tapeworm anthelmintics, antibiotics, and an approved heartworm preventative containing ivermectin. Hematology and clinical chemistry values were compared pre- and post-study and were unremarkable.

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

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

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 (spinosad) 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/lb (30 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial tetracyclic macrolides. Spinosad contains two major factors, spinosyn A and spinosyn D, derived from the naturally occurring bacterium, *Saccharopolyspora spinosa*. Spinosyn A and spinosyn D have the chemical compositions 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[5-dimethylamino)-tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione and 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[5-dimethylamino)-tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, respectively.

Indications:
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on dogs and puppies 14 weeks of age and older and 5.0 pounds of body weight or greater.

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

Do not use the dosing schedule below when administering COMFORTIS to cats, as it can result in an underdosage.

Dosage Schedule:

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
5 to 10 lbs	140	One
10.1 to 20 lbs	270	One
20.1 to 40 lbs	560	One
40.1 to 60 lbs	810	One
60.1 to 120* lbs	1620	One

* Dogs over 120 lbs should be administered the appropriate combination of tablets.

Administer COMFORTIS with food for maximum effectiveness.

COMFORTIS is a chewable tablet and is readily consumed by dogs when offered by the owner just prior to feeding. Alternatively, COMFORTIS may be offered in food or administered like other tablet medications. COMFORTIS should be administered at monthly intervals.

If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.

Treatment with COMFORTIS may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of flea season. In areas where fleas are common year-round, monthly treatment with COMFORTIS should continue the entire year without interruption.

To minimize the likelihood of flea 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 concomitant extra-label use of ivermectin with COMFORTIS (see **POST APPROVAL EXPERIENCE**).

Precautions:
COMFORTIS is for use in dogs and puppies 14 weeks of age and older (see **ANIMAL SAFETY**).

Use with caution in breeding females (see **ANIMAL SAFETY**). Use with caution in dogs with pre-existing epilepsy (see **ADVERSE REACTIONS**). The safe use of COMFORTIS in breeding males has not been evaluated.

Adverse Reactions:
In a well-controlled US field study, which included a total of 470 dogs (330 dogs treated with COMFORTIS and 140 dogs treated with an active control), no serious adverse reactions were observed with COMFORTIS. All reactions were regarded as mild and did not result in any dog being removed from the study.

Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence > 1% within any of the 3 months of observation are presented in the following table. The most frequently reported adverse reaction in dogs in the COMFORTIS and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of COMFORTIS.

Percentage of Dogs (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS Chewable Tablets (N=330)	Active Topical Control (N=139[a])	COMFORTIS Chewable Tablets (N=282)	Active Topical Control (N=124)	COMFORTIS Chewable Tablets (N=260)	Active Topical Control (N=125)
Vomiting	12.7	12.2	7.8	3.2	5.8	4.8
Decreased Appetite	9.1	5.0	2.8	1.6	1.9	0.8
Lethargy	7.6	5.0	3.5	4.0	1.2	0.8
Diarrhea	6.7	5.0	4.3	0.8	1.2	0.0
Cough	3.9	5.0	0.4	2.4	0.0	0.0
Polydipsia	2.4	1.4	0.7	0.0	0.4	0.0
Vocalization	1.8	0.0	0.4	0.0	0.4	0.0
Increased Appetite	1.5	0.0	0.4	0.8	0.4	0.0
Erythema	1.5	0.0	0.4	0.0	0.4	0.0
Hyperactivity	1.2	1.4	0.0	0.0	0.4	0.0
Excessive Salivation	1.2	0.0	0.4	0.0	0.0	0.0

[a] This number (n=139) is less than the total number of dogs in the safety population for the active control group (n=140) because one dog joined the study late and was only dosed at Month 3.

In US and European field studies, no dogs experienced seizures when dosed with COMFORTIS at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of COMFORTIS, 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 are listed in decreasing order of frequency: *vomiting, depression/lethargy, anorexia, ataxia, diarrhea, pruritus, trembling, hypersalivation and seizures.*

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 preventatives according to label directions.

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

Mode of Action:
The primary target of action of COMFORTIS in insects is an activation of nicotinic acetylcholine receptors (nAChRs). Spinosad does not interact with known insecticidal binding sites of other nicotinic or GABAergic insecticides such as neonicotinoids, fiproles, milbemycins, avermectins, and cyclodienes. Insects treated with spinosad show involuntary muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosad-induced hyperexcitation results in prostration, paralysis, and flea death. The selective toxicity of spinosad between insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nAChRs.

Effectiveness:
In a well-controlled laboratory study, COMFORTIS 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 99.8% 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/pyodermatitis 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 and 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 6 days of treatment, usually within 2.5 hours of dosing. Treated females lost weight early in the treatment period, but their weights were similar to control dogs by the end of the 24-day study. COMFORTIS was not associated with any clinically significant changes in hematology, blood coagulation or urinalysis parameters; however, mild elevations in ALT occurred in all dogs treated with COMFORTIS. By day 24, ALT values had returned to near baseline levels. Phospholipidosis (vacuolation) of the lymphoid tissue was seen in all dogs treated with COMFORTIS, 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 the control. Increased vomiting was observed at elevated doses, usually within 1 hour following administration. Vomiting at all doses decreased over time and stabilized when puppies were 14 weeks of age. The average daily and total weight gains of treated dogs were smaller than control dogs and were dose dependent. COMFORTIS was not associated with clinically significant changes in hematology, clinical chemistry, coagulation or urinalysis parameters. Phospholipidosis (vacuolation) of the lymphoid tissue was seen in some dogs in the 4.4X group and all dogs in the 7.4X group. The long term effects of phospholipidosis are unknown. Treatment with COMFORTIS 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 for conception rates in the dams, or for mortality, body temperature, necropsy, or histopathology findings for the dams or puppies. One dam from each treatment group experienced early pregnancy loss and one additional high dose dam aborted late term. The treated dams experienced more vomiting, especially at one hour post-dose, than the control dams. Puppies from dams treated at 1.3 times the maximum recommended therapeutic dose had lower body weights than puppies from control dams. Although puppy mortality between treated and control dams was not different, the puppies from the treated dams experienced more lethargy (4.4X group only), dehydration, weakness and felt cold to the touch (4.4X group only) than puppies from control dams.

A pilot study without a control group was conducted to analyze milk from three lactating dogs treated with an experimental formulation of spinosad at 1.5 times the maximum recommended dose administered at day 28 of gestation and 24 hours prior to parturition. The data demonstrated that spinosyns were excreted in the milk of these dogs. Mortality and morbidity were greatest in puppies from the dam with the highest spinosyns level in milk. The spinosad milk: reference plasma exposure ratio calculated from this study ranged from 2.2 to 3.5.

In well-controlled field studies, COMFORTIS was administered safely in conjunction with other frequently used veterinary products, such as vaccines, anthelmintics, antibiotics, steroids, flea and tick control products, anesthetics, NSAIDs, antihistamines, alternative/herbal remedies, shampoos, and prescription diets. Changes in hematology, clinical chemistry and urinalysis values were compared pre- and post-study and were unremarkable.

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

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

Approved by FDA under NADA # 141-277
Manufactured for:
Elanco US Inc.
Greenfield, IN 46140
www.comfortis.com

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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 4.1 pounds of body weight or greater.

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 areas where fleas may occur year-round, 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.
- Make sure your veterinarian is aware of all medications, including over-the-counter (OTC) medications, that you are giving to your cat.

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 administered 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 dose rates, 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 tablet 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 started to kill 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 product to help control the flea population. Female fleas that are living on animals produce eggs that fall from the animal 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. Safety was shown in cats and kittens 14 weeks of age and older, in multiple laboratory studies and a field study in household cats. The safe use of COMFORTIS in breeding, pregnant, or lactating cats has not been evaluated.

What side effects might occur with COMFORTIS?
Like all medications, sometimes side effects may occur. In some cases, cats vomited after receiving COMFORTIS. If vomiting occurs within one hour of administration, redose 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, COMFORTIS has been 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 68 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 http://www.fda.gov/reportanimalae

COMFORTIS™-Dogs
(spinosad)

Chewable Tablets

Your veterinarian has chosen to prescribe COMFORTIS to meet your flea treatment and prevention 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 5.0 pounds of body weight or greater.

Why has my veterinarian prescribed COMFORTIS?
Your veterinarian has provided this medication to either prevent a flea infestation or to treat an existing infestation on your dog.

What should I discuss with my veterinarian regarding COMFORTIS for my dog?
Your veterinarian is your dog's healthcare expert and can make the best recommendation for medications for your dog. 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 areas where fleas may occur year-round, 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 dog?
Give COMFORTIS with food for maximum effectiveness.

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

Give COMFORTIS to your dog 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 dog?
COMFORTIS has been tested in many types of dogs, and no severe adverse reactions have been reported. At elevated dose rates, the most severe adverse reaction observed was increased vomiting. In the event of a possible overdose, contact your veterinarian, who is the healthcare expert for your dog.

Should I restrict either my dog's activity or contact with my dog after the tablet is consumed?
Since COMFORTIS is an oral formulation, you may maintain normal activities and interactions with your dog.

How quickly will COMFORTIS kill fleas?
In a laboratory study, COMFORTIS started to kill fleas within 30 minutes and killed 100% of the fleas within 4 hours. COMFORTIS kills fleas before they can lay eggs.

Does seeing fleas on my dog mean that the flea 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 product to help control the flea population.

Female fleas that are living on animals produce eggs that fall from the animal 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 dog. 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 dog's environment.

Regardless of the product used to kill the fleas, the dog can continue to be exposed to the fleas that live in the environment. When these fleas jump onto the dog, they will be quickly killed by COMFORTIS.

If you see fleas on your dog within a month after your dog receives COMFORTIS, it is most likely that these are new fleas that have very recently emerged from pupae and jumped onto the dog. These new fleas will quickly be killed before they can produce eggs that contaminate the environment.

Is it safe to give my dog COMFORTIS?
COMFORTIS has been demonstrated to be safe in pure and mixed breeds of healthy dogs when used according to label directions. Safety was shown in puppies 14 weeks of age and older and adult dogs in both laboratory studies and clinical field studies. You should discuss the use of COMFORTIS with your veterinarian prior to use if your dog has a history of epilepsy (seizures).

Is it safe to give my breeding dogs COMFORTIS?
Use with caution in breeding females. You should discuss the use of COMFORTIS with your veterinarian prior to use in breeding females. Safe use of COMFORTIS in male dogs intended for breeding has not been evaluated.

What side effects might occur with COMFORTIS?
Like all medications, sometimes side effects may occur. In some cases, dogs vomited after receiving COMFORTIS. If vomiting occurs within an hour of administration, redose with another full dose. During clinical studies, no severe or prolonged vomiting occurred. Additional adverse reactions observed in the clinical studies were decreased appetite, lethargy or decreased activity, diarrhea, cough, increased thirst, vocalization, increased appetite, redness of the skin, hyperactivity and excessive salivation. These reactions were regarded as mild and did not result in any dog being removed from the studies. Since the introduction of COMFORTIS, additional side effects reported are incoordination, itching, trembling and seizures.

Can other medications be given while my dog is taking COMFORTIS?
Yes, COMFORTIS has been given safely with a wide variety of products and medications. Your veterinarian should be made aware of all products that you administered and/or intend to administer to your dog. For heartworm prevention, use products that are specifically prescribed by your veterinarian.

How should COMFORTIS be stored?
Store at 68-77°F (20-25°C). Temporary periods of time outside of this range between 59-86°F (15-30°C) are permitted.

If you have questions regarding the use of this product, consult your veterinarian, your dog'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 http://www.fda.gov/reportanimalae

Revised: August 2020

Elanco™

Credelio Quattro™

(lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Flavored Chewable Tablets
For oral use in dogs only

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

DESCRIPTION
Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) are flavored chewable tablets available in five sizes for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide minimum doses of 9 mg/lb (20 mg/kg) lotilaner, 0.009 mg/lb (0.02 mg/kg) moxidectin, 2.28 mg/lb (5 mg/kg) praziquantel, and 2.28 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

Lotilaner is a member of the isoxazoline class of parasiticides and the chemical name is 5-[(5S)-4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-3-methyl-N-[2-oxo-2-[(2,2,2-trifluoroethyl) amino]ethyl]- 2-thiophenecarboxamide.

Moxidectin is a semisynthetic macrocyclic lactone derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus.* The chemical name for moxidectin is [6R,23E,25S(E)]-5-O- demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)- 6,28-epoxy-23-(methoxyimino) milbemycin B.

Praziquantel is an isoquinolone anthelmintic with the chemical name 2-(cyclohexylcarbonyl)-1,2,3,6,7,-11b-hexahydro-4H-pyrazino [2,1- a]isoquinolin-4-one.

Pyrantel is a member of the tetrahydropyrimidine family of compounds. Its chemical name is (E)- 1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl) vinyl] pyrimidine 4, 4' methylenebis [3-hydroxy-2-naphthoate](1:1).

INDICATIONS
Credelio Quattro is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*), hookworm (adult *Uncinaria stenocephala*), and tapeworm (*Dipylidium caninum, Taenia pisiformis,* and *Echinococcus granulosus*) infections. Credelio Quattro 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 3.3 pounds or greater.

DOSAGE AND ADMINISTRATION
Credelio Quattro is given orally once a month, at the minimum dosage of 9 mg/lb (20 mg/kg) lotilaner, 0.009 mg/lb (0.02 mg/kg) moxidectin, 2.28 mg/lb (5 mg/kg) praziquantel, and 2.28 mg/lb (5 mg/kg) pyrantel (as pamoate salt). Credelio Quattro must be administered with food (see **Clinical Pharmacology**). Care should be taken to ensure that the dog consumes the complete dose and that part of the dose is not lost or refused. If vomiting occurs within an hour after administration, readminister a new dose of Credelio Quattro. If a dose is missed, give Credelio Quattro immediately and resume a monthly dosing schedule.

Dosing Schedule:

Body Weight (lbs)	Tablets to Administer	Lotilaner per Tablet (mg)	Moxidectin per Tablet (mg)	Praziquantel per Tablet (mg)	Pyrantel* per Tablet (mg)
3.3 – 6	1	56.25	0.056	14.25	14.25
6.1 – 12	1	112.5	0.113	28.5	28.5
12.1 – 25	1	225	0.225	57	57
25.1 – 50	1	450	0.45	114	114
50.1 – 100	1	900	0.9	228	228
> 100	Administer the appropriate combination of tablets				

*As pamoate salt

Heartworm Prevention
Credelio Quattro should be administered year-round at monthly intervals or at least within 1 month of the animal's first seasonal exposure to mosquitoes and continuing until at least 1 month after the dog's last seasonal exposure. If a dose is missed, give Credelio Quattro immediately and resume monthly dosing. When replacing a monthly heartworm preventive product, Credelio Quattro should be given within 1 month of the last dose of the former medication.

Intestinal Nematode and Cestode Treatment and Control
Credelio Quattro should be administered as a single dose for the treatment of roundworm, hookworm, and tapeworm infections.
Monthly use of Credelio Quattro will control any subsequent infections. Dogs may be exposed to and can become infected with gastrointestinal worms throughout the year, regardless of season or climate. Clients should be advised of appropriate measures to prevent reinfection of their dog with intestinal parasites.

Flea Treatment and Prevention
Treatment with Credelio Quattro should be administered year-round at monthly intervals or started at least 1 month before fleas become active. To minimize the likelihood of flea re-infestation, it is important to treat all dogs and cats within a household with a flea control product.

Tick Treatment and Control
Treatment with Credelio Quattro can begin at any time of the year. Credelio Quattro should be administered year-round at monthly intervals or started at least 1 month before ticks become active.

CONTRAINDICATIONS
There are no known contraindications for the use of Credelio Quattro.

WARNINGS
Not for use in humans. Keep this and all drugs out of reach of children. Wash hands after handling. If accidentally ingested, seek medical attention immediately.

Keep Credelio Quattro in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS
Lotilaner, one of the ingredients in Credelio Quattro, 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.

Prior to administration of Credelio Quattro, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. Credelio Quattro is not effective against adult *D. immitis*.

The safe use of Credelio Quattro in breeding, pregnant, or lactating dogs has not been evaluated.

ADVERSE REACTIONS
In a field safety and effectiveness study, Credelio Quattro was administered to dogs for the prevention of heartworm disease.
The study included a total of 372 dogs treated once monthly for up to 11 treatments (191 treated with Credelio Quattro and 181 treated with an active control). Over the 330-day study period, all observations of potential adverse reactions were recorded.

Adverse reactions seen during the field study are summarized in the table below.

Dogs with Adverse Reactions in the Field Study

Clinical Sign	Credelio Quattro N=191 Number (Percentage)	Active Control N=181 Number (Percentage)
Diarrhea, with or without blood*	21 (11%)	15 (8.3%)
Vomiting	18 (9.4%)	8 (4.4%)
Lethargy	12 (6.3%)	1 (0.6%)
Anorexia	11 (5.8%)	5 (2.8%)
Dermatitis	10 (5.2%)	8 (4.4%)
Weight Loss	6 (3.1%)	3 (1.7%)
Pruritus (itching)	3 (1.6%)	1 (0.6%)
Alopecia (hair loss)	2 (1.0%)	4 (2.2%)
Seizure	1 (0.5%)	4 (2.2%)
Ataxia	1 (0.5%)	1 (0.6%)
Nystagmus	1 (0.5%)	0 (0.0%)
Anisocoria	1 (0.5%)	1 (0.6%)

*Four dogs administered Credelio Quattro and five dogs administered the active control had bloody diarrhea.

One geriatric dog receiving Credelio Quattro experienced two episodes of vomiting, ataxia, and nystagmus, 11 days apart, with the first episode occurring two days after the eighth dose. The dog recovered within 24 hours after the first episode and 1 hour after the second episode and completed the study. One dog receiving Credelio Quattro was observed by the investigator to have anisocoria during scheduled physical examinations one month after the ninth dose and one month after the eleventh dose.

In a U.S. field study, 165 dogs received a combination of lotilaner, moxidectin, and praziquantel, three of the active ingredients at the same doses as in Credelio Quattro, monthly for up to 11 months. Two dogs with no history of seizures experienced seizures during the study. One of the dogs developed cluster seizures and was removed from the study. Ataxia was also observed in one other dog three days after the first dose.

In a U.S. field study, one dog administered lotilaner alone, a component of Credelio Quattro, was observed with intermittent head tremors within 1.5 hours of administration of vaccines, an ear cleaning performed by the owner, and its first dose of lotilaner.
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 lotilaner alone.

The dog recovered without treatment and completed the study. In a U.S. field study, two dogs with a history of seizures received lotilaner alone and experienced no seizures throughout the study.

CONTACT INFORMATION

For a copy of the Safety Data Sheet (SDS) 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 http://www.fda.gov/reportanimalae.

INFORMATION FOR ANIMAL OWNER

Echinococcus granulosus is a tapeworm found in wild canids and domestic dogs. *E. granulosus* can infect humans and cause serious disease (hydatid disease). Owners of dogs living in areas where *E. granulosus* is endemic should be instructed on how to minimize their risk of exposure to this parasite, as well as their dog's risk of exposure. Although Credelio Quattro was 100% effective in laboratory studies in dogs against *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of hydatid disease in humans.

CLINICAL PHARMACOLOGY

Mechanism of Action

Credelio Quattro contains four active pharmaceutical ingredients, lotilaner, moxidectin, praziquantel, and pyrantel (as pamoate salt).

Lotilaner is an ectoparasiticide 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.

Moxidectin is an endectocide in the macrocyclic lactone class. Moxidectin acts by interfering with the chloride channel-mediated neurotransmission in the parasite. This results in paralysis and death of the parasite.

Praziquantel's mode of action is not precisely known, but treated tapeworms undergo muscular paralysis accompanied by a rapid influx of calcium ions and the disruption of the tegument.

Pyrantel is a nematocide belonging to the tetrahydropyrimidine class. Pyrantel acts as a depolarizing, neuromuscular-blocking agent in susceptible parasites, causing paralysis and death or expulsion of the parasite.

Pharmacokinetics

Due to reduced drug bioavailability of lotilaner in the fasted state, Credelio Quattro must be administered with a meal or within 30 minutes after feeding.

Following a single oral administration of Credelio Quattro at the minimum labeled dose in the fed state or a single intravenous administration of 5 mg lotilaner, 0.005 mg moxidectin, 1.25 mg praziquantel, and 1.25 mg pyrantel per kg body weight to Beagle dogs (1.5 to 2.5 years old), the mean oral bioavailability for lotilaner, praziquantel, and pyrantel was 93%, 41%, and 31%, respectively. Bioavailability for moxidectin is not reported due to insufficient data to adequately describe the elimination phase following intravenous administration. For Credelio Quattro, the area under the curve from time of dosing to the time of the last measurable concentration (AUC_{last}) was 5970, 1.75, 1.54, and 0.857 mg*h/L for lotilaner, moxidectin, praziquantel, and pyrantel, respectively. Peak concentrations (C_{max}) of 9070, 15.3, 390, and 122 ng/mL were reached (T_{max}) 10, 4.5, 0.75, and 2.5 h after dosing for lotilaner, moxidectin, praziquantel, and pyrantel, respectively. Mean plasma elimination half-lives were 806, 634, 3.64, and 4.87 h for lotilaner, moxidectin, praziquantel, and pyrantel, respectively.

Following nine oral administrations of Credelio Quattro at 1X, 3X, and 5X the maximum labeled dose of 40 mg/kg lotilaner, 0.04 mg/kg moxidectin, 10 mg/kg praziquantel, and 10 mg/kg pyrantel, every 28 days in 8-week-old Beagle dogs, moxidectin and lotilaner area under the curve from time of dosing to the time of the last measurable concentration (AUC_{last}) increased approximately in a less than proportional manner, whereas praziquantel AUC_{last} increased approximately in a more than proportional manner from 1X to 5X after most study doses. Pyrantel AUC_{last} increased approximately in a proportional manner from 1X to 5X observed after first, sixth, and last doses. Within the 1X group, accumulation was observed between Days 0 and 224 with geometric mean accumulation ratios for AUC_{last} of 6.2 and 7.9 for lotilaner and moxidectin, respectively. Concentrations of praziquantel and pyrantel prior to each dose were below the limit of quantification.

EFFECTIVENESS

Heartworm Prevention

In two well-controlled laboratory studies, a single oral dose of Credelio Quattro was 100% effective in preventing the development of adult *D. immitis* in dogs inoculated with infective larvae 30 days before administration.

In a well-controlled U.S. field study consisting of 156 dogs administered Credelio Quattro and 149 administered an active control for 11 consecutive months, no dogs treated with Credelio Quattro tested positive for heartworm disease. All dogs treated with Credelio Quattro were negative for *D. immitis* antigen and blood microfilariae at study completion on Day 330.

Intestinal Nematode and Cestode Treatment and Control

In well-controlled laboratory studies, a single dose of Credelio Quattro was ≥ 97.0% effective against immature adult and adult *Toxocara canis*, adult *Toxascaris leonina,* and adult *Uncinaria stenocephala* infections.

In well-controlled laboratory studies, a single dose of Credelio Quattro was 100% effective against *Echinococcus granulosus*.

In separate well-controlled laboratory studies, praziquantel alone was 100% effective against *Echinococcus granulosus, Dipylidium caninum,* and *Taenia pisiformis*.

Flea Treatment and Prevention

In a well-controlled laboratory study, Credelio Quattro was 100% effective against adult fleas 24 hours after administration or infestation for 36 days. In a separate laboratory study, lotilaner alone began to kill fleas 4 hours after administration or infestation, with greater than 99% of fleas killed within 8 hours after administration or infestation for 35 days.

In a well-controlled U.S. field study conducted in households with existing flea infestations of varying severity, flea reductions of 99.5% to 100% were observed over the course of three monthly treatments with lotilaner alone. 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.

Tick Treatment and Control

In well-controlled laboratory studies, Credelio Quattro was ≥ 97.1% effective against *Rhipicephalus sanguineus* ticks 48 hours after administration or infestation for 32 days. In well-controlled laboratory studies, lotilaner alone was > 97% effective 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, lotilaner alone started killing *Ixodes ricinus* ticks within 4 hours after administration.

Palatability: In the U.S. field study, which included 552 doses administered to 191 dogs, dogs voluntarily consumed 59.8% of Credelio Quattro doses from an empty bowl, on the floor, or when offered by hand, and an additional 28.4% of doses when offered with food. The administration of 11.8% of doses required placement of the chewable tablet in the back of the dog's mouth. All doses were administered within 30 minutes of a meal.

TARGET ANIMAL SAFETY

Margin of Safety

Credelio Quattro was administered orally at 0X, 1X, 3X, and 5X the maximum labeled doses at 28-day intervals for nine treatments to 32 healthy, 8-week-old Beagle puppies. Dogs in the control group received placebo. Credelio Quattro-related clinical chemistry findings included increased bile acids in two of the 3X dogs. Minimal mononuclear cell infiltration of the liver was noted microscopically in five control dogs, two 1X dogs, three 3X dogs, and five 5X dogs. One control dog, one 1X dog, two 3X dogs, and none of the 5X dogs also had minimal extramedullary hematopoiesis. Credelio Quattro-related clinical observations included a dose-dependent increase in discolored feces, diarrhea, and vomiting. All dogs recovered without treatment. Hypersalivation associated with vomiting on the day of dosing occurred in two of the 5X dogs.

Avermectin Sensitive Collie Safety

Credelio Quattro was administered orally at 0X, 1X, 2X, and 5X the maximum labeled dose at 28-day intervals for three treatments to 32 healthy, avermectin sensitive Collie dogs. Dogs in the control group received a vehicle control. One dog in each of the control, 2X, and 5X groups had transient mild depression. Salivation and vomiting was observed in a dose-dependent manner in the 1X, 2X, and 5X groups. Diarrhea, with or without blood, was observed in all groups, including controls, and resolved without treatment.

Heartworm Positive Safety

Credelio Quattro was administered orally at 0X, 1X, and 3X the maximum labeled dose at 28-day intervals for three treatments to 24 healthy, Beagle dogs with patent adult heartworm infections and circulating microfilariae. Dogs in the control group received placebo. Diarrhea and/or vomiting occurred in all dogs in the 3X group at various times up to 12 hours post-dose. Diarrhea occurred in fewer dogs in the 1X and control groups. All dogs experiencing post-dose gastrointestinal issues recovered without treatment. Hypersensitivity reactions (e.g., anaphylaxis, shock, collapse, respiratory distress, or depression) were not observed in any dog.

Field Safety

In a well-controlled field study, Credelio Quattro was used concurrently with other medications such as vaccines, antimicrobials, anthelmintics, antiemetics, steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetics, and analgesics. No adverse reactions were associated with the concurrent use of Credelio Quattro and other medications.

HOW SUPPLIED

Credelio Quattro (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is available in five strengths of flavored chewable tablets formulated according to the weight of the dog (see **Dosage and Administration**). Each chewable tablet size is available in packages of 1, 6, or 12 tablets.

STORAGE INFORMATION

Store at 15-25°C (59-77°F). Excursions permitted between 5 and 40°C (41 and 104°F).

Approved by FDA under NADA # 141-581

Manufactured for: Elanco US Inc, Greenfield, IN 46140

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June 2024

Credelio™
(lotilaner)

Chewable Tablets

For oral use in dogs

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

Description:
CREDELIO (lotilaner) is a beef-flavored, chewable tablet for oral administration to dogs and puppies according to their weight. Each chewable tablet is formulated to provide a minimum lotilaner dosage of 9 mg/lb (20 mg/kg).

Lotilaner has the chemical composition of 5-[(5S)-4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-3-methyl-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-2-thiophenecarboxamide.

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:

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

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

Adverse Reaction (AR)	CREDELIO Group: Number (and Percent) of Dogs with the AR (n=198)	Active Control Group: Number (and Percent) of Dogs with the AR (n=86)
Weight Loss	3 (1.5%)	2 (2.3%)
Elevated Blood Urea Nitrogen (BUN)	2 (1.0%)*	0 (0.0%)
Polyuria	2 (1.0%)*	0 (0.0%)
Diarrhea	2 (1.0%)	2 (2.3%)

*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 polyuria 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.

Post-Approval Experience (2023):
The following adverse events are based on post-approval adverse drug experience reporting for CREDELIO. 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 exposure using these data.

The following adverse events reported in dogs are listed in decreasing order of reporting frequency:

Vomiting, diarrhea (with and without blood), lethargy, anorexia, seizure, pruritus, ataxia, urinary-related signs (polyuria, polydipsia, urinary incontinence, and inappropriate urination), and muscle tremor.

Contact Information:
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.

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 ectoparasiticide 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.com
Rev. date 02/2024

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Elanco™

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-didehydromilbemycins in the ratio of approximately 80% A_4 ($C_{32}H_{45}NO_7$, MW 555.71) and 20% A_3 ($C_{31}H_{43}NO_7$, MW 541.68).

Package color	Milbemycin oxime tablet
Brown	2.3 mg*
Green	5.75 mg
Yellow	11.5 mg
White	23.0 mg

*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

Body Weight	INTERCEPTOR
2-10 lbs.	One tablet (2.3 mg)
11-25 lbs.	One tablet (5.75 mg)
26-50 lbs.	One tablet (11.5 mg)
51-100 lbs.	One tablet (23.0 mg)

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 given within 30 days after the last dose of DEC.

Palatability: Palatability trials conducted in 244 dogs from 10 different U.S. veterinary practices demonstrated that INTERCEPTOR was willingly accepted from 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 larvae and the adult stage of hookworm (*Ancylostoma caninum*), roundworms (*Toxocara canis*, *Toxascaris leonina*) and whipworm (*Trichuris vulpis*) infestations when administered orally according to the recommended dosage schedule.The anthelmintic activity of milbemycin oxime is believed to be a result of interference with invertebrate neurotransmission.

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, anthelmintics, antibiotics, steroids, flea collars, shampoos and dips.

Two studies in heartworm-infected dogs were conducted which demonstrated mild, transient hypersensitivity reactions in treated dogs with high microfilaremia counts (see Precautions for reactions observed). Safety studies in pregnant dogs demonstrated that high doses (1.5 mg/kg =3X) of milbemycin oxime 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 (25X 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.

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-didehydromilbemycins in the ratio of approximately 80% A_4 ($C_{32}H_{45}NO_7$, MW 555.71) and 20% A_3 ($C_{31}H_{43}NO_7$, 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

Body Weight	INTERCEPTOR
1.5 to 6 lbs.	One tablet (5.75 mg)
6.1-12 lbs.	One tablet (11.5 mg)
12.1-25 lbs.	One tablet (23.0 mg)

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. The tablets can be broken for ease of administration. Watch the cat 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 for Cats must be administered monthly, preferably on the same date each month. The first dose should be administered within one month of the cat'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 for Cats immediately and resume the monthly dosing schedule. It is recommended that cats be tested for existing heartworm infection prior to starting treatment with INTERCEPTOR for Cats (see Precautions).

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 the tablet in the cat's mouth or placed the tablet in the cat's food in 72% of cats. 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 eliminate the tissue stage of heartworm larvae and hookworm (*Ancylostoma tubaeforme*) and roundworm (*Toxocara cati*) infections when administered orally according to the recommended dosage schedule.The anthelmintic activity of milbemycin oxime is believed to be a result of interference with invertebrate neuro- transmission.

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, anthelmintics, anesthetics, antibiotics, steroids, flea collars, shampoos and dips.

Safety studies were conducted in young cats and kittens and doses of 1X, 3X and 5X the minimum recommended dose of 2.0 mg/kg demonstrated no drug-related effects. Tolerability studies at exaggerated doses of 10X also demonstrated no drug-related adverse effects in kittens and young adult 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

Elanco™

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 the oxime derivatives of 5-didehydromilbemycins in the ratio of approximately 80% A_4 ($C_{32}H_{45}NO_7$, MW 555.71) and 20% A_3 ($C_{31}H_{43}NO_7$, MW 541.68).
Milbemycin oxime is classified as a macrocyclic anthelmintic.
Praziquantel is an isoquinolone anthelmintic with the chemical name 2-(Cyclohexylcarbonyl)-1,2,3,6,7,-11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.

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**).

Dosage Schedule

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

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 first 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:
Dogs may be exposed to and can become infected with roundworms, whipworms, hookworms, and tapeworms throughout the year, regardless of season or climate. Clients should be advised of appropriate measures to prevent reinfection of their dog with intestinal parasites. 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.

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

Warnings
Not for use in humans. Keep this and all drugs out of the reach of children.

Precautions
Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see **EFFECTIVENESS**).
Prior to administration of INTERCEPTOR PLUS, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. INTERCEPTOR PLUS is not effective against adult *D. immitis*.
Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.
Do not use in puppies less than six weeks of age.
Do not use in dogs or puppies less than two pounds of body weight.
The safety of INTERCEPTOR PLUS has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime alone (see **ANIMAL SAFETY**).

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 parasites, as well as their dog's risk of exposure. Although INTERCEPTOR PLUS (milbemycine 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 Safety
INTERCEPTOR PLUS:
In a repeated dose safety study, 40 ten-week-old puppies (10 per group) were dosed with either a sham dose (0X) or 1, 3, or 5X the maximum label exposure of INTERCEPTOR PLUS every 14 days for a total of seven treatments. Ataxia, lethargy, and salivation 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 (0X) 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 dose. 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 microfilariae 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 before 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 (5X 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.
Greenfield, IN 46140, USA
Approved by FDA under NADA # 141-338

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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 dose of 13.5 mg/lb (30 mg/kg) and a minimum milbemycin oxime dose of 0.2 mg/lb (0.5 mg/kg). Spinosad is a member of the spinosyns class of insecticides, which are non-antibacterial tetracyclic macrolides. Spinosad contains two major factors, spinosyn A and spinosyn D, derived from the naturally occurring bacterium, *Saccharopolyspora spinosa*. Spinosyn A and spinosyn D have the chemical compositions $C_{41}H_{65}NO_{10}$ and $C_{42}H_{67}NO_{10}$, respectively. Milbemycin oxime is a macrocyclic lactone anthelmintic, containing two major factors, A_3 and A_4 of milbemycin oxime. The approximate ratio of A_3:A_4 is 20:80. Milbemycin A_4 5-oxime has the chemical composition of $C_{32}H_{45}NO_7$ and milbemycin A_3 5-oxime has the chemical composition of $C_{31}H_{43}NO_7$.

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 (*Ancylostoma caninum*), adult roundworm (*Toxocara canis* and *Toxascaris leonina*) and adult whipworm (*Trichuris vulpis*) infections in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater.

Dosage and Administration: TRIFEXIS is given orally, once a month at the minimum dosage of 13.5 mg/lb (30 mg/kg) spinosad and 0.2 mg/lb (0.5 mg/kg) milbemycin oxime body weight.

For heartworm prevention, give once monthly for at least 3 months after exposure to mosquitoes (see **EFFECTIVENESS**).

Dosage Schedule:

Body Weight	Spinosad Per Tablet (mg)	Milbemycin oxime Per Tablet (mg)	Tablets Administered
5 to 10 lbs	140	2.3	One
10.1 to 20 lbs	270	4.5	One
20.1 to 40 lbs	560	9.3	One
40.1 to 60 lbs	810	13.5	One
60.1 to 120 lbs	1620	27	One
Over 120 lbs	Administer the appropriate combination of tablets		

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

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

Flea Treatment and Prevention: Treatment with TRIFEXIS may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of 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, whipworms and hookworms throughout the year, regardless of season or climate. Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

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

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

Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS (see **ADVERSE REACTIONS**).

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

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

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

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

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

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

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

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

Average Monthly Rate (%) of Dogs With Adverse Reactions

Adverse Reaction	TRIFEXIS Chewable Tablets[a]	Active Control Tablets[a]
Vomiting	6.13	3.08
Pruritus	4.00	4.91
Lethargy	2.63	1.54
Diarrhea	2.25	1.54
Dermatitis	1.47	1.45
Skin Reddening	1.37	1.26
Decreased appetite	1.27	1.35
Pinnal Reddening	1.18	0.87

[a]n=176 dogs

In the US field study, one dog administered TRIFEXIS experienced a single mild seizure 2 ½ hours after receiving the second monthly dose. The dog remained enrolled and received four additional monthly doses after the event and completed the study without further incident.

Following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS, some dogs have experienced the following clinical signs: *trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation*. Spinosad alone has been shown to be safe when administered concurrently with heartworm preventatives at label directions.

In US and European field studies, no dogs experienced seizures when dosed with spinosad alone at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of spinosad, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

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

Post Approval Experience (Mar 2012): The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, pruritus, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening.

Mode of Action: The primary target of action of spinosad, a component of TRIFEXIS, is an activation of nicotinic acetylcholine receptors (nAChRs) in insects. Spinosad does not interact with known insecticidal binding sites of other nicotinic or GABAergic insecticides such as neonicotinoids, fiproles, milbemycins, avermectins and cyclodienes. Insects treated with spinosad show involuntary muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosad-induced hyperexcitation results in prostration, paralysis and flea death. The selective toxicity of spinosad between insects and vertebrates may be conferred by the differential sensitivity of the insect versus vertebrate nAChRs.

Milbemycin oxime, a component of TRIFEXIS, acts by binding to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells. Increased permeability by the cell membrane to chloride ions causes hyperpolarization of affected cells and subsequent paralysis and death of the intended parasites. Milbemycin oxime may also act by disrupting the transmission of invertebrate neurotransmitters, notably gamma amino butyric acid (GABA).

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

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

Flea Treatment and Prevention: In a well-controlled laboratory study, TRIFEXIS demonstrated 100% effectiveness on the first day following treatment and 100% effectiveness on Day 30. In a well-controlled laboratory study, spinosad, a component of TRIFEXIS, began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. Spinosad, a component of TRIFEXIS, kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with spinosad alone. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis and pruritus as a direct result of eliminating the fleas.

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

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

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

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

Body weights were similar between control and treated groups throughout the study. Treatment with TRIFEXIS was not associated with any clinically significant hematology, clinical chemistry or gross necropsy changes. One 5X dog had minimal glomerular lipidosis observed microscopically. The clinical relevance of this finding is unknown.

Plasma spinosyn A, spinosyn D, milbemycin A_3 5-oxime and milbemycin A_4 5-oxime concentrations increased throughout the study. At each dosing period, plasma spinosyn A and spinosyn D concentrations were greater than proportional across the dose range 1 to 5X.

Plasma milbemycin A_4 5-oxime concentrations appeared to be dose proportional across range 1 to 5X by the end of the study.
Plasma concentrations of spinosad and milbemycin oxime indicate that expected systemic exposures were achieved throughout the study.
In an avermectin-sensitive Collie dog study, TRIFEXIS was administered orally at 1, 3, and 5 times the upper half of the recommended therapeutic dose band every 28 days. No signs of avermectin sensitivity were observed after administration of TRIFEXIS during the study period to avermectin-sensitive Collie dogs. The adverse reactions observed in the treatment groups were vomiting and diarrhea. Body weights in all treatment groups were comparable to the control group. Hematology and clinical chemistry parameters showed no clinically significant changes from study start to end, and all dogs were considered healthy throughout the study.
In a heartworm positive safety study, TRIFEXIS was administered orally at 1, 3, and 5 times the upper half of the therapeutic dose band to Beagle dogs with adult heartworm infections and circulating microfilariae, every 28 days for 3 treatments. Vomiting was observed in one dog in the 1X group, in three dogs in the 3X group, and in one dog in the 5X group. All but one incident of vomiting was observed on the treatment day during the first treatment cycle. The vomiting was mild and self-limiting. Hypersensitivity reactions were not observed in any of the treatment groups. Microfilariae counts decreased with treatment.
In a reproductive safety study, TRIFEXIS was administered orally to female dogs at 1 and 3 times the upper half of the therapeutic dose band every 28 days prior to mating, during gestation and during a six-week lactation period. Dogs with confirmed fetal heartbeats on ultrasound examination were evaluated for reproductive safety. One 3X and one 1X group female did not become pregnant.
No treatment-related adverse reactions or signs of avermectin toxicosis were noted for adult females. Adult females in the 3X group lost weight during the 6-week pre-mating period, while control group females gained weight during that time. The body weights of the treated groups were comparable to the control group during gestation and post-parturition phases of the study. Gestation length, litter average body weight, litter size, stillborn pups, pup survival and the proportion of pups with malformations were comparable between treated and control dam groups. Malformations in the 1X group included a pup with cleft palate and a littermate with anophthalmia, fused single nares, misshapen palate, hydrocephalus, omphalocele and malpositioned testes; a pup with a malformation of the anterior tip of the urinary bladder and umbilical blood vessel; and a pup with patent ductus arteriosus (PDA). Malformations in the 3X group included three littermates with PDA. Malformations in the control group included a pup with a malformed sternum and a pup with PDA and a malpositioned superior vena cava. Clinical findings in pups of the treated groups were comparable to the control group except for one 1X group pup that was smaller and less coordinated than its littermates and had tremors when excited. The relationship between spinosad and milbemycin oxime treatment and the 1X and 3X dogs that did not become pregnant, the specific pup malformations and the unthrifty 1X group pup are unknown. The incidence of cleft palate is not unexpected based on the historical data collected at the breeding site.
In a margin of safety study with spinosad alone, 6-week old Beagle puppies were administered average doses of 1.5, 4.4, and 7.4 times the maximum recommended dose at 28-day intervals over a 6-month period. Vomiting was observed across all treatments, including controls, and was observed at an increased rate at elevated doses. Vomiting most often occurred 1 hour following administration and decreased over time and stabilized when puppies reached 14 weeks of age.
Storage Information: Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).
How Supplied: TRIFEXIS is available in five tablet sizes. Each tablet size is available in color-coded packages of 6 tablets.
5-10 lbs (140 mg spinosad and 2.3 mg milbemycin oxime)
10.1-20 lbs (270 mg spinosad and 4.5 mg milbemycin oxime)
20.1-40 lbs (560 mg spinosad and 9.3 mg milbemycin oxime)
40.1-60 lbs (810 mg spinosad and 13.5 mg milbemycin oxime)
60.1-120 lbs (1620 mg spinosad and 27 mg milbemycin oxime)
Approved by FDA under NADA # 141-321
Manufactured for:
Elanco US Inc.
Greenfield, IN 46140
Revised: May 2020

Information for Dog Owners

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

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

Why has my veterinarian prescribed TRIFEXIS?
Your veterinarian has prescribed TRIFEXIS as a way of preventing your dog from developing problems caused by infection with three commonly occurring parasite categories. **Heartworm infection** can make dogs very sick and can even be fatal. This parasite is spread to dogs by mosquitoes. TRIFEXIS can prevent **flea infestations** from becoming established, and can also remove any fleas that are on your dog at the time of treatment. TRIFEXIS will also treat and control common adult **intestinal worm infections** (roundworms, hookworms and whipworms).

Should I give TRIFEXIS each month all year round?
Consult your veterinarian regarding the need for year round use of TRIFEXIS. If you do not administer TRIFEXIS monthly throughout the year, the final dose must be given no fewer than three months following the last exposure to mosquitoes.

Will TRIFEXIS kill heartworms?
TRIFEXIS prevents heartworm disease by killing certain stages that develop after an infected mosquito bites a dog. As with other heartworm preventatives, TRIFEXIS does not kill adult heartworms. Speak to your veterinarian about treatment options if your dog is diagnosed with an adult heartworm infection.

Will my dog still need to be tested for heartworm infection while taking TRIFEXIS?
You should speak to your veterinarian about the frequency of heartworm testing while your dog is taking TRIFEXIS.

How do I switch to TRIFEXIS from another heartworm preventative?
Follow the advice of your veterinarian about switching heartworm preventatives.

What should I discuss with my veterinarian regarding TRIFEXIS for my dog?
Your veterinarian is your dog's healthcare expert and can make the best recommendation for medications for your dog. This includes the prevention, control and/or treatment of parasites such as fleas, heartworms and intestinal parasites that may cause conditions that include flea allergy dermatitis, anemia and heart disease. Key points of your discussion may include the following:

- As with other heartworm preventatives, dogs should be tested for heartworm prior to beginning treatment with TRIFEXIS.
- If a dose is missed and a monthly interval between doses is exceeded, then immediately give TRIFEXIS with food and resume monthly dosing. This practice will minimize the opportunity for heartworms to grow. Also, continuing normal monthly dosing will allow you to gain control of any flea or intestinal parasites that might have infected your dog.
- To minimize the likelihood of fleas continuing to jump onto your dog, it is important to treat all household pets with an approved flea protection product.
- TRIFEXIS is not for use in humans. Like all medications, keep TRIFEXIS out of reach of children.

How should I give TRIFEXIS to my dog?
Give TRIFEXIS with food for maximum effectiveness. TRIFEXIS is a chewable tablet and may be offered as a treat. Consult your veterinarian regarding the need for year round administration of TRIFEXIS. 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 TRIFEXIS to my dog?
Contact your veterinarian as soon as possible if you believe your dog has ingested more than the recommended dose of TRIFEXIS. In a study in which dogs were dosed at 1, 3, and 5 times the upper half of the recommended dose, dogs exhibited vomiting, tremors, decreased activity, salivation, coughing and vocalization.

Should I restrict either my dog's activity or contact with my dog after the tablet is consumed?
Since TRIFEXIS is an oral formulation, you may maintain normal activities and interactions with your dog.

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

Does seeing fleas on my dog mean that the treatment is not working?
TRIFEXIS kills fleas before they can lay eggs when used monthly according to the label directions. Remember that all animals in the household should be treated with an approved flea product to help control the flea population.
Your dog can continue to be exposed to the fleas that live in the environment. When fleas jump onto your dog, they will be killed by TRIFEXIS.
If within a month after your dog receives TRIFEXIS you see fleas on your dog, it is most likely that these are new fleas. These new fleas will be killed before they can produce eggs that contaminate the environment. Continued monthly use of TRIFEXIS can prevent any new infestations.

What if I see worms in my dog's stool during the month after administration of TRIFEXIS?
TRIFEXIS is indicated to treat and control intestinal parasite infections of adult hookworms, roundworms and whipworms. In occasional cases, it is possible that the action of TRIFEXIS in killing the intestinal worms will lead to the dog expelling them in the stool. If you have questions, consult with your veterinarian for measures you can take to prevent a reinfection with intestinal parasites.

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

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

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

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

How should TRIFEXIS be stored?
Store at 68-77°F (20-25°C). Temporary periods of time outside this range between 59-86°F (15 -30°C) are permitted.
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