

THE MISSING LINK *Triatoma gerstaeckeri* is the most common triatomine species in the south-central United States and a vector for *Trypanosoma cruzi*, a protozoal organism that causes Chagas disease.

PARASITOLOGY

Chagas Disease: *Trypanosoma cruzi* Infection in Dogs

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Chagas disease is caused by *Trypanosoma cruzi*, a protozoal organism primarily transmitted by triatomine insect vectors, also known as “kissing bugs.” It is a zoonotic disease originally described by Brazilian physician Dr. Carlos Chagas in 1909 and is widespread in Latin America. Although triatomines and *T. cruzi* have long been endemic to the southern United States, awareness and identification of infected vectors and animals have recently increased throughout the United States. Canine Chagas disease can be acute or chronic and is predominantly characterized by inflammation and fibrosis of the heart, resulting in arrhythmias, myocardial dysfunction, heart failure, and sudden death, although many infected dogs are asymptomatic.

High densities of dogs in confined areas are associated with heat and carbon dioxide, which attract kissing bugs.

TRIATOMINE VECTORS

Triatomine insect vectors belong to the family Reduviidae, subfamily Triatominae (FIGURE 1). In the southern United States, 11 triatomine species are established; species regularly encountered by people and dogs include *Triatoma gerstaeckeri*, *Triatoma sanguisuga*, *Triatoma rubida*, and *Triatoma recurva* (FIGURE 2).¹ In contrast to the domesticated species found in Central and South America, which live in human dwellings, many triatomines of the southern United States are considered to be sylvatic (associated with wildlife and natural habitats) and only occasionally drawn into the domestic and peridomestic environments. Colonization of homes by triatomines in the United States is often associated with rustic or dilapidated housing, or with the *T. recurva* species in Arizona.²

Triatomine insects feed primarily on blood. They are generalist feeders and obtain blood meals from many hosts, predominantly vertebrates (e.g., wild/domestic mammals, birds, amphibians, reptiles, humans); they have also been shown to feed on invertebrates (e.g., crickets).

Infection prevalence of *T. cruzi* in triatomines ranges from approximately 20% to 70% depending on species, with an overall 54% infection prevalence reported



FIGURE 1. Life stages of *Triatoma gerstaeckeri*, the most common triatomine species in the south-central United States. From left to right: eggs; first through fifth instar nymphal stages; adult female (note the pointed ovipositor at the base of the abdomen); adult male. Each life stage takes multiple blood meals from multiple hosts before molting to the next life stage. Triatomines are generally differentiated from other morphologically similar insects based on dark bodies overall, often with red or orange lines along the sides of the abdomen; thin, dark legs; and expanded mouthparts (rostrum) between the antennae, giving a “cone-nose” appearance. For help identifying kissing bugs, or to submit a triatomine for free *Trypanosoma cruzi* testing, please visit the Texas A&M University Kissing Bug Citizen Science Program website (kissingbug.tamu.edu).

across specimens from 17 states (predominantly Texas) submitted to a Kissing Bug Citizen Science program.³

Risk factors for *T. cruzi* infection include living in or traveling to an area with infected insect vectors.⁴ All dogs are at risk for infection; however, dogs with lifestyles that include outdoor work or housing can have increased risk of exposure.⁴⁻⁶ Dog kennels may be

particularly suitable environments for the establishment of *T. cruzi* transmission cycles. High densities of dogs in confined areas are associated with heat and carbon dioxide, which attract kissing bugs. For example, nearly 40% of triatomines collected by members of the public and submitted to a Kissing Bug Citizen Science program were collected from kennel environments.³

Several insects appear similar to the kissing bug and cause confusion among the public and veterinary community (BOX 1). These “look-alike” insects do not feed on blood from humans or animals (although some are associated with painful bites) and pose no risk for the transmission of *T. cruzi*.

TRYPANOSOMA CRUZI

Life Cycle

The morphologic forms of the *T. cruzi* parasite include amastigotes, epimastigotes, and trypomastigotes. Amastigotes are found in mammalian host cells, and epimastigotes live in the hindgut of the triatomine insect. Both replicate by binary fission. Trypomastigotes are present in the bloodstream of mammalian hosts during acute infection and can be seen in blood smears (FIGURE 3). Infective trypomastigotes are also present in the hindgut and feces of the triatomine insect vector.

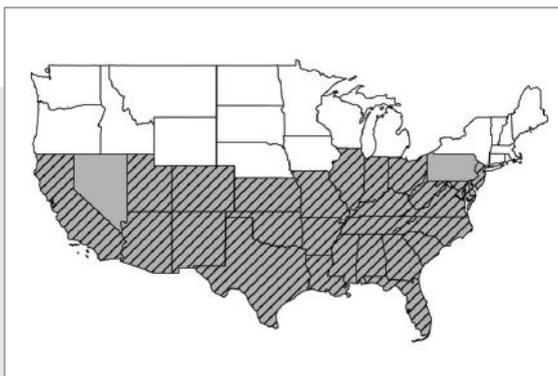


FIGURE 2. Triatomines are distributed across the southern half of the United States, where dogs are at risk for becoming locally infected with *T. cruzi*. All shaded states have at least one historical record of triatomines. Striped states are those in which the Texas A&M Kissing Bug Citizen Science Program has received at least one submission of a triatomine encountered by a member of the public. Although triatomines are primarily reported in southern states, infected dogs with travel histories are found in northern states.

BOX 1 Look-Alike Species Commonly Mistaken For Kissing Bugs

Some of the most common insects that look similar to kissing bugs, yet pose no risk of *T. cruzi* transmission, include (A) the wheel bug, (B) *Zelus longipes*, and (C) *Leptoglossus brevisrostris*. For help identifying kissing bugs, or to submit a triatomine for free *Trypanosoma cruzi* testing, please visit the Texas A&M University Kissing Bug Citizen Science Program website (kissingbug.tamu.edu).



Transmission

The *T. cruzi* parasite is transmitted through the stercorarian (vector-fecal) route when a kissing bug excretes the parasite in its fecal material onto the host and the parasite enters through the bite wound, a break in the skin, or a mucous membrane. Although this method of transmission is inefficient,⁷ an epidemiologic setting with insects that colonize the home and feed night after night is a high-risk scenario for vector-fecal transmission to humans. Oral transmission can occur after consumption of fruit or juices contaminated with triatomine feces or through consumption of infected insects, as has been shown in experimental lab studies with raccoons.⁸ The relative importance of stercorarian versus oral transmission in dogs is unknown.

Nonvector routes of parasite transmission include transplacental and transmammary from infected mother to offspring (human, animal), blood transfusion (human), ingestion of an infected animal (human, animal),⁹ and rare laboratory accident (human). In pregnant women with antibodies to *T. cruzi*, the global rate of transmission is estimated to be 4.7%,¹⁰ while a corresponding estimate for veterinary congenital transmission is unknown.

In nature, many wild and domestic animals are involved in maintaining the *T. cruzi* transmission cycle. Hundreds of mammalian species, including dogs, can become infected with *T. cruzi*. Birds, reptiles, and amphibians, however, are incompetent hosts. The most commonly studied *T. cruzi* hosts in the southern United States include raccoons, woodrats, opossums, and dogs.¹¹ Domestic cats are increasingly recognized as

infected and potentially clinically affected hosts.¹² The relative importance of different reservoir hosts—that is, species that become infected and serve as a source of infection to feeding triatomines—likely varies geographically. In South America, dogs and cats are recognized as parasite reservoirs,¹³ but their importance as reservoirs in the United States is unknown.

Prevalence

Prevalence of *T. cruzi* infection among dogs ranges depending on canine population and type of serologic test used. For example, antibodies against *T. cruzi* were detected in 18% and 7% of shelter dogs in Texas and Louisiana, respectively.^{14,15} In a study of dogs housed in kennels in central Texas where triatomines were abundant, seroprevalence exceeded 50%.¹⁶

CHAGAS DISEASE

Distribution

Chagas disease is prevalent in Latin America and is increasingly recognized in the United States. In areas where triatomines are established, infections may be acquired from local vectors.¹⁷ However, Chagas disease is not geographically confined to regions where triatomines live, so human medical and veterinary providers may encounter patients with Chagas disease outside traditionally endemic environments.¹⁸ Travel and relocation of animals have the potential to redistribute infected dogs; for example, in one study, government working dogs that provide security and border protection in northern states tested positive for



T. cruzi, likely reflecting infections acquired when the dogs trained in southern states.¹⁹ Consequently, Chagas disease should be considered in the differential diagnosis for unexplained arrhythmias and myocardial dysfunction in dogs with unknown origin or travel history or known travel to endemic regions.

Clinical Presentation

The progression of Chagas disease in dogs is similar to that in humans. Inflammation, fibrosis, and cellular damage are caused by trypomastigotes invading host cells to become pseudocysts of intracellular amastigotes. Inflammation is more pronounced in the acute stage, developing into fibrosis in the chronic stage, at which point amastigotes are much less likely to be identified. While the heart is the organ primarily affected in dogs, parasites can be found in many other tissues (e.g., liver, kidney, spleen, brain, skeletal muscle, lymph node).^{20,21} Information about progression of disease in naturally infected dogs is expanding with continued study.²²

Acute disease develops within approximately 21 days of infection, followed by an indeterminate, asymptomatic phase that can progress into chronic disease. In experimental *T. cruzi* infections, dogs developed chronic disease 8 to 36 months after inoculation.²³ Dogs with acute and chronic disease often remain undiagnosed and are asymptomatic or have only mild clinical signs such as fever, lethargy, lymph node enlargement, and organomegaly (spleen, liver).^{21,23}

Cardiac abnormalities develop in both acute and chronic disease, with damage resulting in arrhythmias, conduction abnormalities, heart enlargement, myocardial dysfunction, heart failure, and sudden death.^{4,20,22-24} Clinical signs include weakness, lethargy, collapse, and signs of congestive heart failure (e.g., abdominal distention, respiratory difficulty).^{4,21,23,24} Physical examination findings support the presence of heart disease, characterized most often as tachycardia/bradycardia, weak or irregular pulses, murmur, dyspnea, and ascites.

Diagnosis

Chagas disease is a diagnostic differential for dogs with arrhythmias, myocardial dysfunction, and congestive heart failure. It can present with findings similar to those of dilated cardiomyopathy (idiopathic, nutritional deficiency), arrhythmogenic right ventricular cardiomyopathy, other forms of infectious

Domestic cats are increasingly recognized as infected and potentially clinically affected hosts.¹²

myocarditis, and congenital tricuspid valve dysplasia.²⁰ The index of suspicion for Chagas disease increases in dogs from an endemic location or that have originated from, traveled to, or are currently living in an area where Chagas disease has been reported.⁴ Testing should be considered for dogs with a mother, littermate, or housemate (dog or cat) that has tested positive for *T. cruzi* infection. As there is no gold standard test, the sensitivity and specificity of the available tests are unknown.

Microscopy

Identification of trypomastigotes on a buffy coat or whole blood smear (**FIGURE 3**) can enable a positive diagnosis of an acute infection when serologic test results are negative early in the disease process. Trypomastigotes and amastigotes can be identified during thorough microscopic examination of needle aspirates of enlarged lymph nodes or, more often, on histopathologic sections of the heart (**FIGURE 4**) or other organs (e.g., spleen, liver, kidney, lymph node, diaphragm).^{20,21}

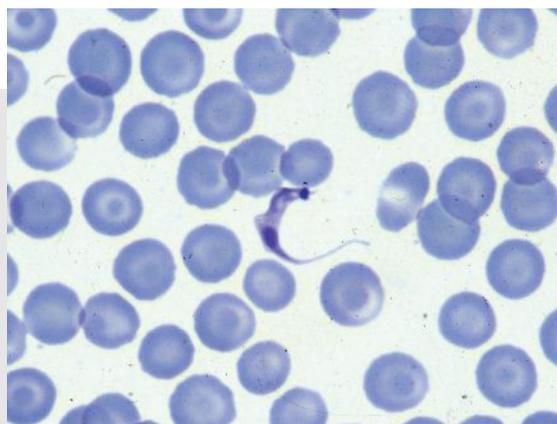


FIGURE 3. Blood-stage *T. cruzi* trypomastigote in a blood smear of an infected dog from Fort Worth, Texas.

Serology

Indirect fluorescent antibody testing, currently available at the Texas A&M Veterinary Medical Diagnostic Laboratory, is the most accessible test for *T. cruzi* infection in dogs. It confirms exposure to the parasite, often indicating current infection because infections are thought to be lifelong.²³ A correlation between titer result and clinical disease has not been established. False negatives are possible during an acute infection within the first month of exposure, and cross-reactivity with *Leishmania* is possible. In human medicine, diagnosis of Chagas disease is a challenge, and multiple independent testing platforms are commonly used to look for consensus in results.¹⁷ Rapid tests that detect antibodies to *T. cruzi* for the diagnosis of Chagas disease in humans are not currently approved for clinical use in animals.

Polymerase Chain Reaction Testing

Polymerase chain reaction (PCR) testing is used to detect parasite DNA in blood and tissue.²⁵ Antemortem testing of blood samples can detect circulating trypomastigotes more likely to be present in acute infections, but test results are limited by the amount of circulating organism present. In chronic disease, PCR results are limited by the low probability that a dog has circulating trypomastigotes. For these reasons, a negative PCR result should not be interpreted to indicate that the host is uninfected and alone is of limited utility as a test of cure. Postmortem PCR testing can be useful to confirm the presence of the organism in tissue samples (e.g., cardiac tissue).

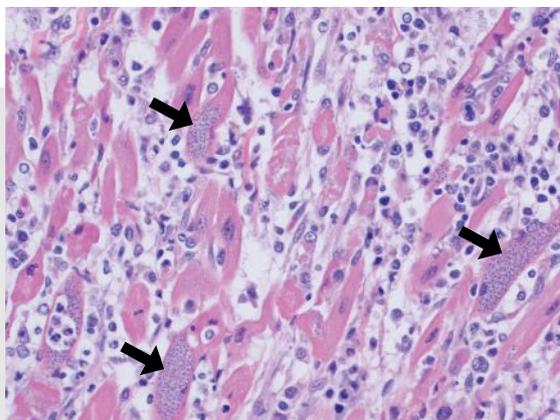


FIGURE 4. Histologic sample from the right ventricle in a dog with *T. cruzi* infection. Pseudocysts of amastigotes (**bold arrows**) are present in multiple cardiomyocytes, which are disrupted by diffuse lymphoplasmacytic inflammation. Hematoxylin-eosin stain, 40× magnification.

Medical Tests for Heart Disease

Diagnostic tests for heart disease include electrocardiography (ECG), echocardiography, and cardiac troponin I. Screening for heart disease in asymptomatic dogs provides information about heart function and arrhythmias that may be clinically silent but increase the risk of clinical signs and sudden death. In dogs with *T. cruzi* infection, ECG abnormalities vary widely based on the location and extent of myocardial damage and resultant inflammation and fibrosis but include changes to the ECG complex, conduction disturbances (atrioventricular block, bundle branch block), and both brady- and tachyarrhythmias.^{4,20,21,24} Infected dogs are more likely to have ventricular arrhythmias and combinations of ECG abnormalities.⁴ An ambulatory ECG (Holter monitor) recording can detect arrhythmias not present during physical examination.⁴

A recent study using Holter monitoring of serologically positive and negative working dogs along the Texas-Mexico border showed that 78% of positive dogs and 11% of negative dogs had ECG abnormalities, most commonly supraventricular and ventricular arrhythmias and atrioventricular block.²²

Echocardiographic abnormalities include enlargement of all 4 heart chambers and ventricular systolic dysfunction. Elevations in cardiac troponin I, a nonspecific indicator of myocardial damage, are reported in dogs infected with *T. cruzi*.^{4,22}

Treatment

Antiprotozoal treatment protocols are not well established in dogs. Prospective studies that include risk-benefit assessment and further investigation into optimal timing and dose of medications are needed to help improve the long-term clinical course of Chagas disease. Anti-trypansomal medications (e.g., benznidazole, nifurtimox, itraconazole) used specifically to treat *T. cruzi* infection may show promise but do not currently have consistently proven efficacy for curing Chagas disease in dogs or preventing the chronic fibrosis and progressive myocardial dysfunction that develops in dogs or humans.^{17,26} These medications have been associated with temporary suppression of parasitemia and have a range of side effects.¹⁷ Additionally, treatment response in dogs may be *T. cruzi* strain dependent.²⁶



Benznidazole treatment in humans and dogs has shown variable clinical benefit and a high possibility of adverse effects, and the medication is not readily available for dogs in the United States.^{17,26} The combined use of itraconazole and the antiarrhythmic medication amiodarone has been described in the treatment of serologically positive dogs.²⁷

Although complex, additional prospective investigation to determine therapeutic protocols, evaluate adverse effects, and establish diagnostic test strategies to assess potential cure and clinical response in symptomatic and asymptomatic naturally infected dogs would be useful.

Medical therapy is tailored to the clinical abnormalities identified in an individual dog, which are most often related to the heart. These include antiarrhythmics for tachyarrhythmias, pacemaker implantation for bradyarrhythmias, positive inotropic therapy with pimobendan for myocardial dysfunction, and diuretic therapy for heart failure.²⁰ Symptomatic chronic disease requires long-term management.

Prevention

Vector control is an important part of managing disease transmission. Kissing bug habitats include wooded areas, brush piles, nests, and porches.¹ The insects are most active at night, are attracted to lights, and can invade homes and kennels. Vector control can include turning off outdoor lights, cleaning up brush and woodpiles that serve as breeding areas for insects, housing animals inside, and using insecticides. Kissing bug control can be difficult in kennels, particularly in recently developed areas where kennels are surrounded by natural habitats with associated wildlife.

Improving public awareness for dog owners and medical professionals is an important step in infection prevention, vector control, and identification of infected animals. Because of its zoonotic potential, it is important for personnel handling blood and tissue of infected animals to take appropriate safety precautions.

CONCLUSION

Although the insects that transmit *T. cruzi* are primarily reported in the southern half of the United States and across Latin America, any dog with vector contact can be infected, including dogs that live in northern states and have a travel history. Infected animals can be asymptomatic or develop a range of cardiac

complications, including sudden death or chronic disease. Because of the challenges in diagnosis and lack of well-established antiparasitic treatments, Chagas disease is an active area of scientific study. **TVP**

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Mirataz™ (mirtazapine transdermal ointment)

For topical application in cats only. Not for oral or ophthalmic use.

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

Before using this product, please consult the product insert, a summary of which follows:

INDICATION: Mirataz™ is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION: Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days. Wear disposable gloves when applying Mirataz™. Alternate the daily application of Mirataz™ between the left and right inner pinna of the ears. **See Product Insert for complete dosing and administration information.**

CONTRAINDICATIONS: Mirataz™ is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients. Mirataz™ should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS: Not for human use. Keep out of reach of children. **Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure.** After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing. In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention. In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS: Do not administer orally or to the eye. Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See **Animal Safety** in the product insert). Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure. Upon discontinuation of Mirataz™, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat. Mirataz™ has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Mirataz™ has not been evaluated in cats that are intended for breeding, pregnant or lactating cats.

ADVERSE REACTIONS: In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz™ and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. **See Product Insert for complete Adverse Reaction information.** To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

EFFECTIVENESS: The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds. Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear. A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit. At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant (p<0.0001) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

STORAGE: Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED: Mirataz™ is supplied in a 5 gram aluminum tube.

MANUFACTURED FOR:
Kindred Biosciences, Inc.
1555 Bayshore Highway, suite 200
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NADA 141-481, Approved by FDA
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NDC 86078-686-01
REG-MTZBS-008 Rev. 26Apr2018

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Advantage Multi® for Dogs and for Cats (imidacloprid + moxidectin)

BRIEF SUMMARY: Before using Advantage Multi® for Dogs (imidacloprid+moxidectin) or Advantage Multi® for Cats (imidacloprid+moxidectin), please consult the product insert, a summary of which follows:

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

Advantage Multi for Dogs:

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 sites for two (2) hours after application.

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

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 species: Hookworms (*Ancylostoma caninum*) (*Uncinaria stenocephala*), Roundworms (*Toxocara canis*) (*Toxascaris leonina*) and Whipworms (*Trichuris vulpis*).

Advantage Multi for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. **Advantage Multi for Cats** kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. **Advantage Multi for Cats** is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the intestinal parasites species Hookworm (*Ancylostoma tubaeforme*) and Roundworm (*Toxocara cati*). **Ferrets:** **Advantage Multi for Cats** is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. **Advantage Multi for Cats** kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations in ferrets.

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

WARNINGS:

Advantage Multi for Dogs: 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*, the signs may be more severe and may include coma and death†.

* 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 Cattle crosses.

† Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.

Advantage Multi for Cats: Do not use on sick, debilitated, or underweight cats. Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight. Do not use on sick or debilitated ferrets.

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. Dogs: Children should not come in contact with the application sites for two (2) hours after application. Cats: Children should not come in contact with the application site for 30 minutes after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with 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 a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

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

Cats may experience hypersalivation, tremors, vomiting and decreased appetite if Advantage Multi for Cats is inadvertently administered orally or through grooming/licking of the application site. The safety of Advantage Multi for Cats has not been established in breeding, pregnant, or lactating cats. The effectiveness of Advantage Multi for Cats against heartworm infections (*D. immitis*) after bathing has not been evaluated in cats. Use of this product in geriatric cats with subclinical conditions has not been adequately studied. Ferrets: The safety of Advantage Multi for Cats has not been established in breeding, pregnant, and lactating ferrets. Treatment of ferrets weighing less than 2.0 lbs. (0.9kg) should be based on a risk-benefit assessment. The effectiveness of Advantage Multi for Cats in ferrets weighing over 4.4 lbs. (2.0 kg) has not been established.

ADVERSE REACTIONS: Heartworm Negative Dogs: The most common adverse reactions observed during field studies were pruritus, residue, medicinal odor, lethargy, inappetence and hyperactivity. **Heartworm Positive Dogs:** The most common adverse reactions observed during field studies were cough, lethargy, vomiting, diarrhea (including hematuria), and inappetence. **Cats:** The most common adverse reactions observed during field studies were lethargy, behavioral changes, discomfort, hypersalivation, polydipsia and coughing and gagging. **Ferrets:** The most common adverse reactions observed during field studies were pruritus/scratching, scabbing, redness, wounds and inflammation at the treatment site, lethargy, and chemical odor.

For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

Advantage Multi is protected by one or more of the following U.S. patents: 6,232,328 and 6,001,858.

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