

# ProMeris™ for dogs



● A technical manual for veterinarians



FORT DODGE ANIMAL HEALTH

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**P**roMeris for dogs is a low-volume, topical spot-on designed to be applied to dogs 8 weeks and older for the treatment and control of fleas and ticks. ProMeris for dogs contains equal amounts of two active ingredients—metaflumizone and amitraz. Metaflumizone is a semicarbazone insecticide with a novel mode of action that has shown excellent activity against fleas. When metaflumizone is combined with amitraz in ProMeris for dogs, it provides broad-spectrum control of both fleas and ticks.

### **Metaflumizone**

Metaflumizone is a new insecticide that has a novel mode of action compared with other products commonly used in veterinary practice to control fleas. Metaflumizone blocks the influx of sodium required to propagate a nerve impulse along the axon and dendrite of the neuron. These disruptions of neuronal impulses result in reductions in feeding, loss of coordination, paralysis, and death of fleas. Additionally, metaflumizone appears to act initially on an insect's mouthparts, resulting in reduced feeding even before it affects the central nervous system.

The activity of neurologically active insecticides can be divided into two

### **ProMeris for dogs Highlights**

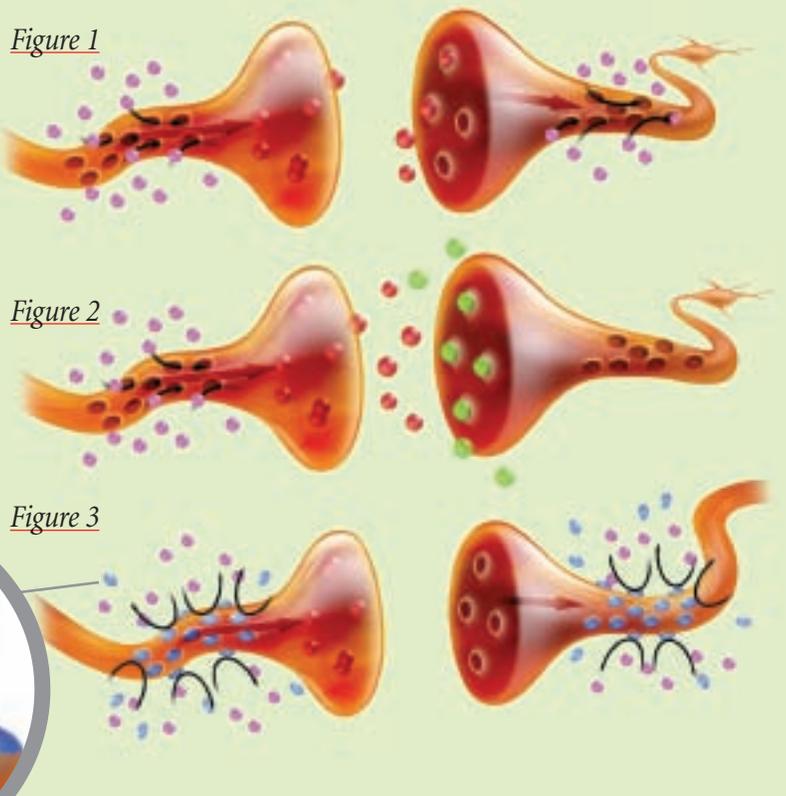
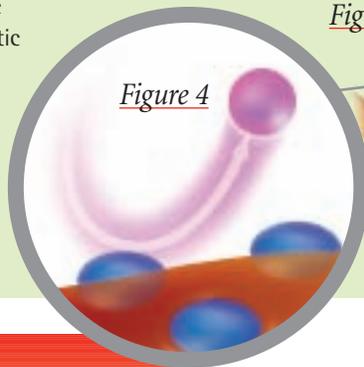
- Contains equal amounts of two active ingredients—metaflumizone and amitraz.
- Provides broad-spectrum control of both fleas and ticks.
- Controls existing flea and tick infestations and protects against reinfestations.
- Kills fleas that may cause flea allergy dermatitis.
- Kills and controls black-legged or deer ticks, brown dog ticks, American dog ticks, and lone star ticks.
- Approved for use on puppies and dogs 8 weeks and older.

**Figure 1—Normal nerve function.** The nerve impulse, represented here by arrows, is propagated by the influx of sodium ions along the axon. When the nerve impulse reaches the synapse, neurotransmitters released from the presynaptic nerve into the synapse are received by the postsynaptic nerve and initiate the influx of sodium ions and the nerve impulse in the postsynaptic nerve.

**Figure 2—Synaptic insecticide.** Synaptic insecticides affect nerve impulse conduction between nerves by attenuating or blocking neurotransmitters.

**Figure 3—Axonal insecticide.** Metaflumizone, an axonal insecticide, stops the nerve impulse by blocking the influx of sodium ions along the axon in both the presynaptic and postsynaptic nerves.

**Figure 4—Metaflumizone activity.** Metaflumizone (blue circles) effectively blocks sodium ions (purple circle).



**Color guide**

- Red circles = neurotransmitters
- Purple circles = sodium ions
- Green circles = synaptic insecticides
- Blue circles = metaflumizone

functional groups depending on where they affect nerve function. One group works in the synapse, and the other group works on the nerve cell axon. In normal nerve function, the influx of sodium into the nerve results in propagation of a nerve impulse. When the impulse reaches the end of the presynaptic nerve, neurotransmitters are released into the synapse. These neurotransmitters bind to the postsynaptic nerve, resulting in generation of the impulse (*Figure 1*).

Synaptic insecticides have many different precise actions, but their impact can be summarized as either blocking or overstimulating synaptic communication. Generally, synaptic insecticides work by mimicking the neurotransmitters from the presynaptic nerve or by blocking or changing the way neurotransmitters interact with the postsynaptic nerve cell (*Figure 2*). Either of these actions results in failure of the postsynaptic nerve to create an impulse, which results in disruption of nerve function.

In contrast, metaflumizone is an axonal insecticide; it binds to voltage-dependent sodium channels in the axon and dendrite of the neuron and blocks the flow of sodium across the neuron's membrane. The nerve impulse then fails to propagate in both presynaptic and postsynaptic nerves, leading to incoordination, paralysis and death of the flea (*Figures 3, 4*).

As these functional groups work by different mechanisms, it is unlikely an insect's resistance to a synaptic insecticide, should it occur, would result in resistance to an axonal insecticide.<sup>1</sup>

## Amitraz

Amitraz is currently approved in many countries for use in domestic animals. In the United States, amitraz is approved for use in topical applications for both food-producing animals and dogs. While its actions are not completely understood, amitraz is generally classified as an inhibitor of the enzyme monoamine oxidase, which is responsible for degrading neurotransmitters including norepinephrine and serotonin. Additionally, amitraz acts as an octopamine agonist, which is a neurotransmitter found in ticks and mites. These neural actions disrupt the normal nerve function of ticks, causing reductions in feeding, loss of coordination, paralysis, lack of attachment and death of ticks.

## Product Uses

ProMeris for dogs can be used to control fleas and ticks on dogs and puppies 8 weeks and older. It is a convenient spot-on product that provides effective control of existing flea and tick infestations and protects against reinfestation.

ProMeris for dogs can also be used to prevent flea infestation of dogs introduced into a flea-contaminated environment. It kills fleas effectively and thus may help to prevent and treat flea allergy dermatitis. ProMeris for dogs kills and controls black-legged or deer ticks (*Ixodes scapularis*), which can transmit *Borrelia burgdorferi*; brown dog ticks (*Rhipicephalus sanguineus*), which can transmit *Ehrlichia canis*; American dog ticks (*Dermacentor variabilis*), which can transmit *Rickettsia rickettsii*; and lone star ticks (*Amblyomma americanum*), which may transmit *Ehrlichia chaffeensis*.

ProMeris for dogs effectively controls fleas for up to six weeks and ticks for up to four weeks. Monthly application is generally recommended for optimal control of these parasites. ProMeris for dogs is waterproof and is effective on indoor and outdoor dogs. ProMeris for dogs can help reduce vector-borne diseases when used as part of a comprehensive external parasite control program.

## Packaging

Each dose of ProMeris for dogs is packaged in an applicator designed to deliver the product directly onto the dog's skin. This process is similar to other available flea control products, so veterinarians and pet owners are familiar with the technology.

<sup>1</sup>Ware GW, Whitacre DM. *The Pesticide Book*. Willoughby, Oh: W.H. Freeman Co, 2004;219-223.

ProMeris for dogs is available in five packaging presentations for different body weights of dogs and puppies 8 weeks and older. Each package contains three or six individual applicator tubes for monthly treatments.

The ProMeris for dog's applicator is designed to provide maximum convenience for pet owners by incorporating several features not available with other flea and tick control product applicators:

- Label information, including weight range, is printed directly on the applicator to ensure pet owners administer the right product to their animal.
  - The applicator nozzle is designed to minimize splash back when opening.
  - The applicator tip presents a rounded interface with the pet's skin when opened to minimize the risk of skin abrasions.
  - The product will not drip out of an open applicator when it is inverted.
- The pet owner must squeeze the applicator slightly to begin administering the product.
- The applicator has a long opening tab for ease of use.
  - The clear plastic composition of the applicator makes it easy to confirm the entire dose has been applied.



## Pharmacokinetics

### Blood levels

Researchers treated adult dogs with the recommended dose of ProMeris for dogs. Plasma samples were taken from all animals five and 10 hours after treatment. Additional plasma samples were taken on Days 1, 2, 3, 5, 7, 10, 14, 21, 28, 42 and 56. A method to measure the levels of both active ingredients in plasma was developed and validated. This method has a lower limit of quantification of 50 ng/ml (ppb) for both metaflumizone and amitraz.

The results of the study demonstrated that only very small amounts of metaflumizone and amitraz are absorbed systemically from dermal application. From Day 0 to Day 5, metaflumizone remained below the level of quantification. From Day 7 until the end of the study, only small quantities (generally less than 100 ng/ml (ppb)) of metaflumizone were found, with peak levels occurring on Day 42. For amitraz, all samples were below the limit of quantification.

XS	≤11 lbs.
S	>11-22 lbs.
M	>22-55 lbs.
L	>55-88 lbs.
XL	>88-110 lbs.

### Hair distribution

Adult dogs were treated according to label recommendations with ProMeris for dogs. Samples of hair were removed from the neck, middle of the back, lumbosacral portion of the back, and right and left thorax on Days 1, 2, 7, 14, 28, 42 and 56. A method to measure the amounts of metaflumizone and amitraz in these samples was developed and validated. All sites were found

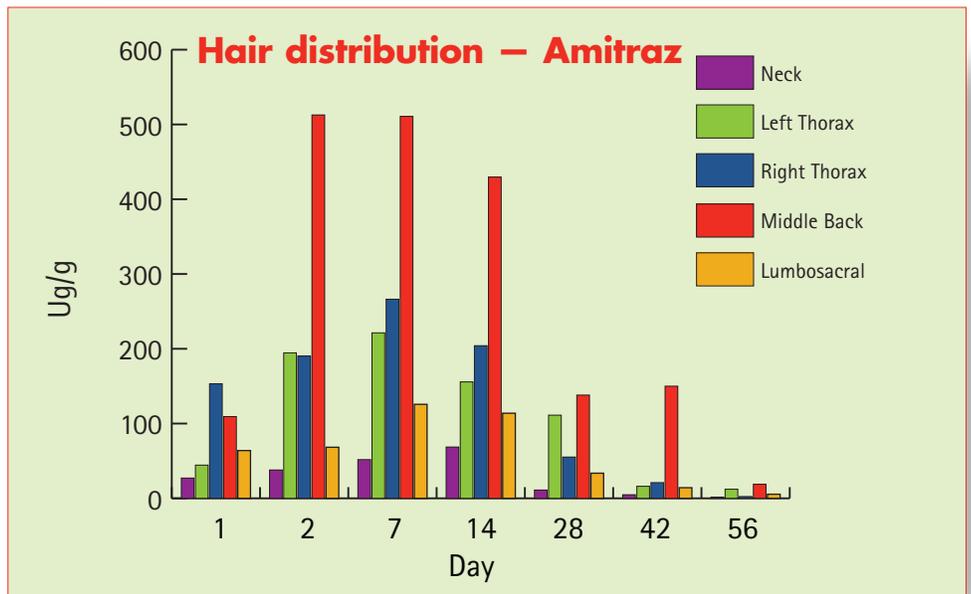
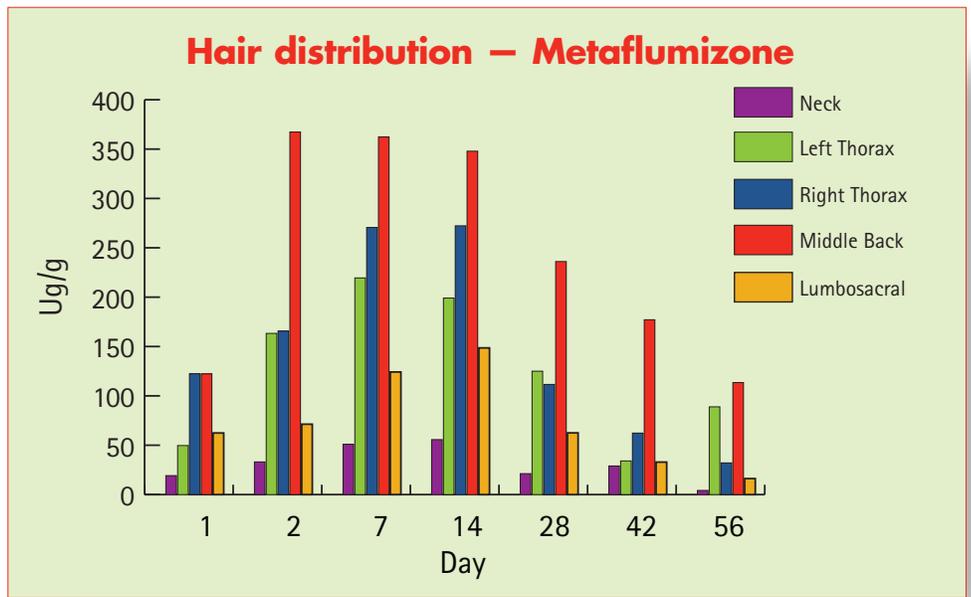
to have levels of both active ingredients on Day 1. These levels generally increased with peak levels found for most sites on Day 14. Levels then slowly decreased to the end of the study. All sites had measurable levels of both active ingredients throughout the study. In contrast, blood levels of both active ingredients were barely detectable, indicating little to no absorption.

These studies prove ProMeris for dogs rapidly distributes on dogs' skin from the site of application and has residual levels in hair during its activity period.

### Safety Studies

The safety profile of ProMeris for dogs has been studied extensively. Multiple exaggerated dose studies were conducted. In these studies, the recommended dose of ProMeris for dogs, three times the recommended dose or five times the recommended dose were topically administered to dogs as young as 8 weeks. In two studies this dosing was performed once, and in one study it was repeated once every two weeks for a total of seven treatments. Following dosing, qualified staff, blinded to study groupings, observed the dogs. Their observations included behavior, food consumption, body weight and results of urinalysis, routine hematology and serum chemistries. During these studies, no clinically significant adverse effects due to treatment with ProMeris for dogs were observed.

In another study, the recommended dose of ProMeris for dogs was administered monthly for four months. Dogs were observed for clinical changes until 30 days following the final treatment. During these studies, no clinically significant adverse effects due to treatment with ProMeris for dogs were observed.



## Comparative effects\*

Active ingredient	Dermal LD <sub>50</sub> mg/kg	Oral LD <sub>50</sub> mg/kg
Metaflumizone	>5,000	>5,000
Imidacloprid	>5,000 <sup>a</sup>	450 <sup>a</sup>
Permethrin	>4,000 <sup>b,c</sup>	430 <sup>c</sup> to 4,000 <sup>c</sup>
Fipronil	>2,000 <sup>d</sup>	97 <sup>d,e</sup>
Amitraz	>1,600	>500

\*LD<sub>50</sub> values are determined in standardized tests in laboratory animals. The LD<sub>50</sub> value is the dose of material resulting in death of 50 percent of the test animals. An LD<sub>50</sub> with a > value generally indicates the study conducted at that dose resulted in less than 50 percent deaths, or the value is the highest dose tested. Generally, larger LD<sub>50</sub> values imply that higher exposures are required to induce fatal toxicity. Due to differences inherent in study protocols and biological variability, small differences in LD<sub>50</sub> values may not be biologically important. These LD<sub>50</sub> values are presented to demonstrate metaflumizone has LD<sub>50</sub> values comparable to other commonly used pesticides.

a-Exttoxnet Imidacloprid, Permethrin 13/4/98, Michigan State University <http://exttoxnet.edu>

b-Exttoxnet Imidacloprid 13/4/1998, Michigan State University <http://exttoxnet.edu>

c-MSDS K9 Advantix® Bayer Animal Health Article Number 2935094.

d-EPA Petition to Establish Tolerance for Pesticides in or on Food CFR August 24, 2005 Number 163. <http://www.epa.gov/fedrgstr/EPA-Pest/2005/August/Day-24/p16807.htm>

e-IPCS-Joint Meeting of FAO and WHO Assessment Group-Fipronil, <http://www.inchem.org/documents/jmpr/jmpmono/v097pr09.htm>

ProMeris for dogs was studied in very small dogs because there is speculation small dogs may be more sensitive to insecticides, and dosing small dogs with a single quantity of an insecticide might expose smaller dogs to a proportionally larger dose. In this study, six Chihuahuas older than 8 weeks and weighing from 1.3 to 4.8 pounds were treated according to label recommendations with a single Extra Small dose of ProMeris for dogs. A second single dose was administered 14 days later. The dogs were observed daily for changes in behavior. Serum chemistry and hematology results were obtained one and seven days after each treatment for 21 days. With the exception of some transitory hyperactivity and pruritus observed in most dogs within the first hour of treatment, no clinically significant adverse responses to treatment were observed.

In studies metaflumizone and amitraz demonstrate low mammalian toxicity following oral exposure in rats, mice and dogs. Reduced weight gain and decreased food consumption were the primary observable adverse effects seen

in dogs treated with chronic exaggerated doses. There are no known mutagenic or carcinogenic effects.

These studies demonstrate ProMeris for dogs delivers the performance veterinarians demand for their patients.

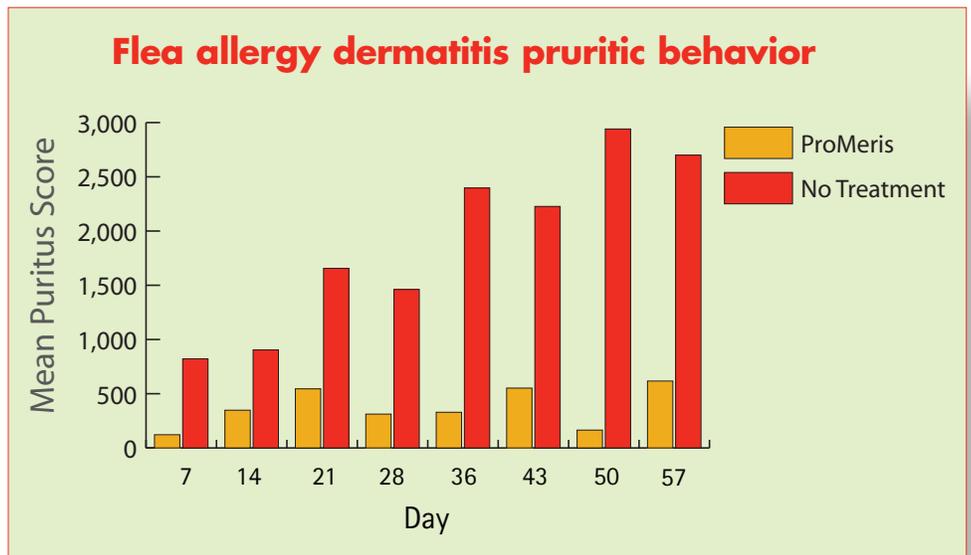
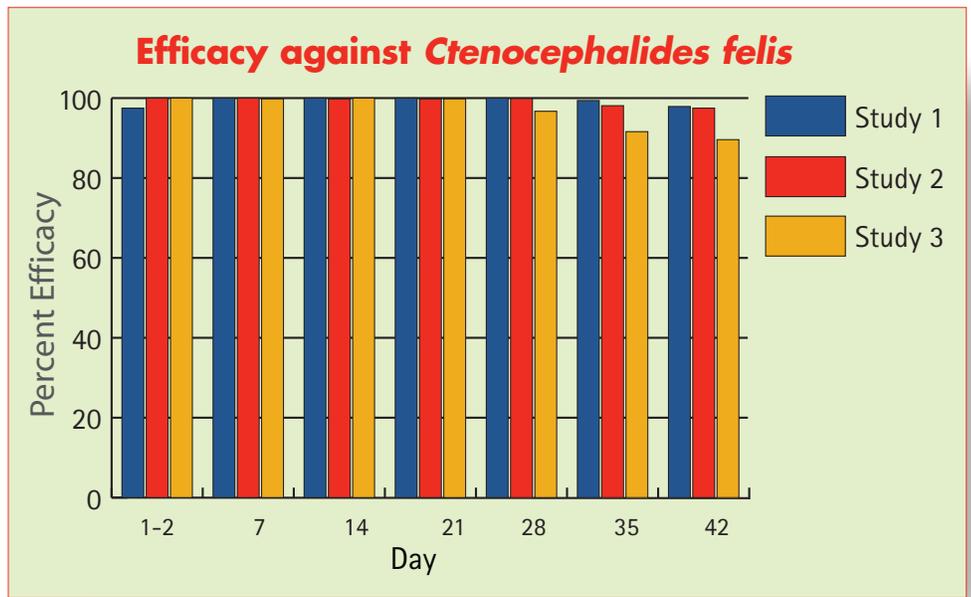
## Canine Efficacy Studies

The studies described in this manual were performed to support the registration of ProMeris for dogs around the world. Some of these studies, including those on mange control, describe findings not found in certain approved product labeling, but they are presented here to demonstrate the data Fort Dodge Animal Health has collected on this product.

### Efficacy study design

Many studies have been conducted to determine the effectiveness of ProMeris for dogs in controlling and killing fleas and ticks. While some specifics of the trials vary, all the presented studies share common character-

istics. In all laboratory studies, healthy purpose-bred dogs were randomly assigned to either a treatment group or a control group. The recommended dose of ProMeris for dogs was administered to the treatment group according to label directions. The control groups were given a placebo or received no treatment. A standard number of fleas or ticks (typically 100 and 50, respectively) were placed on the dogs just before treatment; infestation was repeated weekly. Dogs were inspected for flea and tick burdens using precise standardized methods by qualified observers blinded to study group assignments. The initial evaluation typically occurred 24 to 48 hours after infestation and at given intervals thereafter. To determine efficacy, the number of fleas or ticks found on the nontreated control dogs was compared to the number of fleas or ticks found on the dogs treated with ProMeris for dogs.



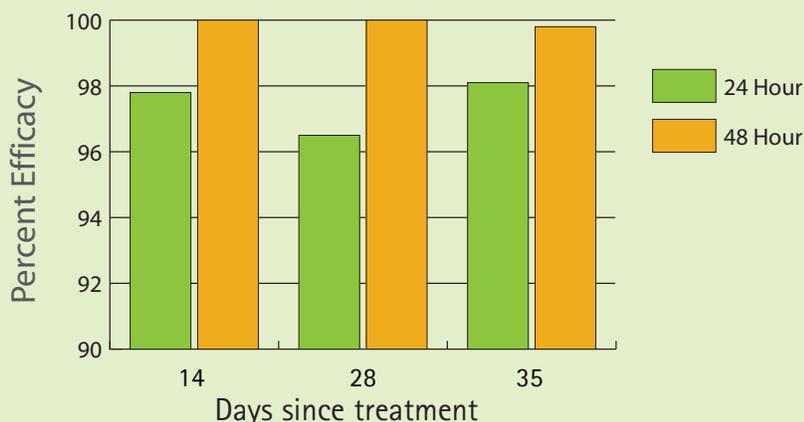
**Efficacy against *Ctenocephalides felis***

Three studies were conducted with essentially identical protocols. In each study, six or eight dogs were treated topically with ProMeris for dogs on Day 0. Dogs were infested with fleas prior to treatment, again on Day 6, and weekly thereafter for six weeks. Observers blinded to treatment groups conducted efficacy evaluations weekly.

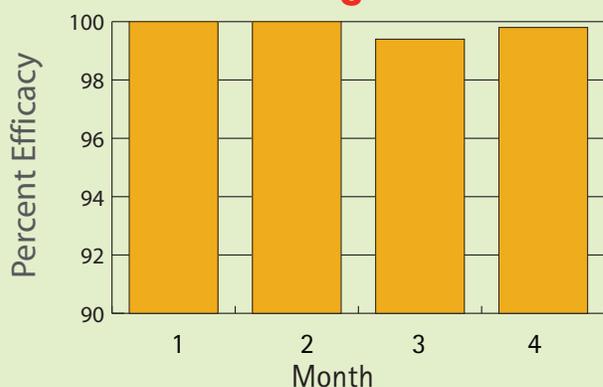
**Effectiveness against signs of flea allergy dermatitis**

Six adult dogs with signs consistent with flea allergy dermatitis were treated according to label directions with ProMeris for dogs on Days 0 and 29. Dogs were infested with fleas before treatment, then weekly for six weeks. Observers blinded to the treatment groups evaluated the dogs weekly. The observers looked for flea infestations, signs of pruritus and skin lesions.

### Efficacy against *C. felis* 24 and 48 hours post-treatment



### Effectiveness of four monthly treatments against *C. felis*



Pruritic behavior was recorded. Signs of skin disease (erythema and skin lesions) were converted to a number score. Fleas were not removed during these evaluations.

In this study, ProMeris for dogs reduced pruritic behavior at all observations, with reductions ranging from 61 to 94 percent. These reductions were statistically significant ( $p < 0.05$ ) on Days 36 through 57. ProMeris for dogs reduced erythema and skin lesion scores at all observations. These reductions ranged from 20 to 30 percent on Day 14 to 61 to 68 percent on Day 57.

### Efficacy against *Ctenocephalides felis* 24 hours post-treatment

Eight adult dogs were treated according to label directions with ProMeris for dogs on Day 0. Dogs were infested with fleas on Days 14, 28, 35 and 42. Efficacy evaluations were performed 24 and 48 hours after each infestation by observers blinded to treatment groupings.

In this study, ProMeris provided greater than 95 percent control of fleas at both 24- and 48-hour evaluations through Day 37.

### Efficacy of four monthly treatments against *Ctenocephalides felis*

Twelve adult dogs were treated according to label directions with ProMeris for dogs on Day 0, then retreated monthly for three months. Dogs were infested with fleas 26 days after each treatment. Efficacy evaluations were conducted two days after each infestation by observers blinded to treatment groups.

In this study, ProMeris for dogs provided greater than 99 percent control of fleas through four months.

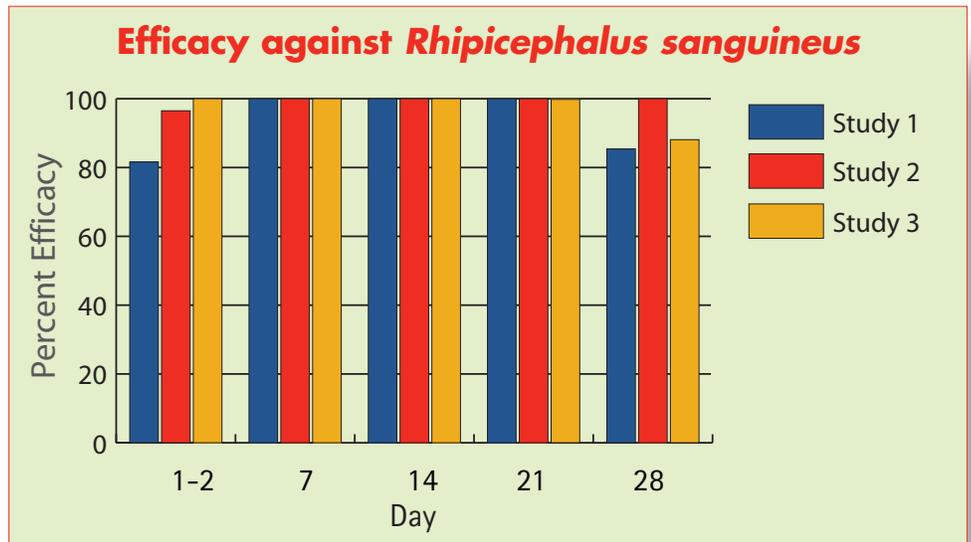
### Efficacy Against Ticks

#### Efficacy against *Rhipicephalus sanguineus* (brown dog tick)

Three studies were conducted with essentially identical protocols. In

each study, six or eight dogs were treated according to label directions with ProMeris for dogs on Day 0. Dogs were infested with ticks (*Rhipicephalus sanguineus*) prior to treatment, on Day 5 and weekly thereafter for four weeks. Observers blinded to treatment groups conducted weekly efficacy evaluations.

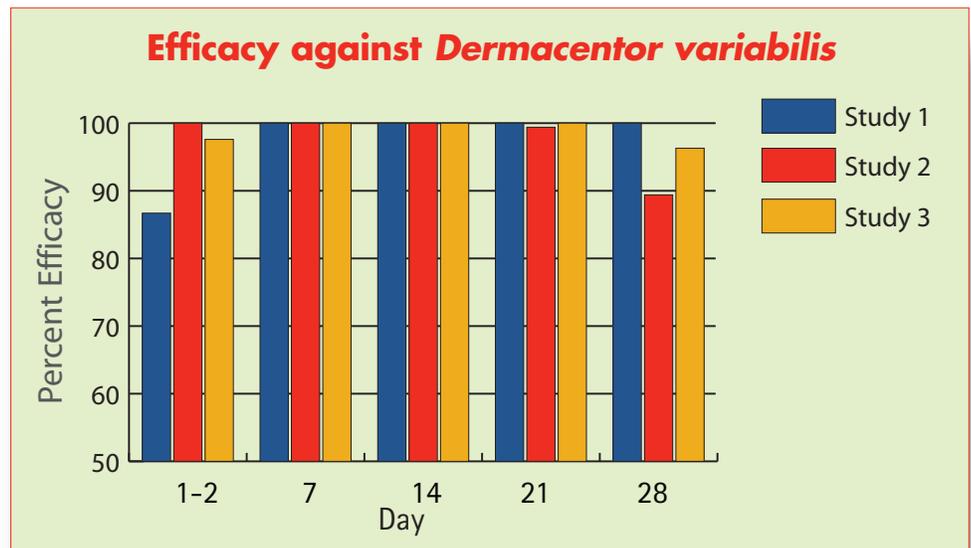
In these studies, ProMeris for dogs provided a high level of tick control through at least Day 28.



### Efficacy against *Dermacentor variabilis* (American dog tick)

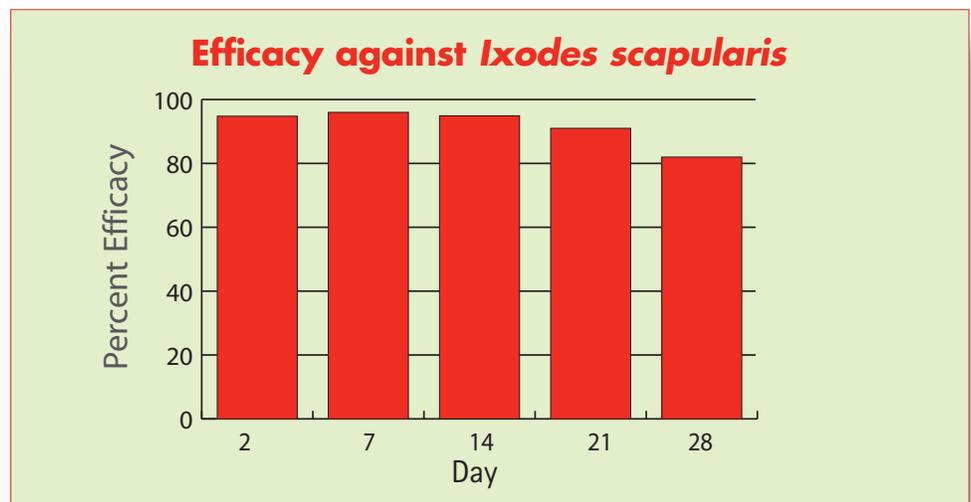
Three studies were conducted with essentially identical protocols. In each study, six or eight dogs were treated according to label directions with ProMeris for dogs on Day 0. Dogs were infested with ticks (*Dermacentor variabilis*) prior to treatment, again on Day 5 and weekly thereafter for four weeks. Observers blinded to treatment groups conducted efficacy evaluations weekly.

In these studies, ProMeris for dogs provided a high level of tick control through at least Day 28.

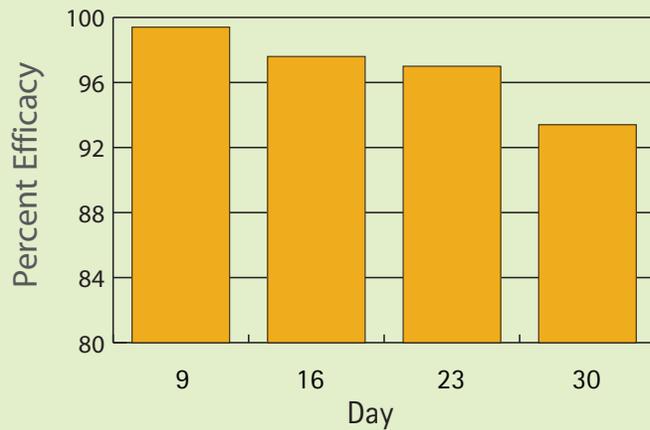


### Efficacy against *Ixodes scapularis* (black-legged or deer tick)

Eight adult dogs were treated according to label directions with ProMeris for dogs on Day 0. Dogs were infested with ticks (*Ixodes scapularis*) before treatment, again on Day 5 and weekly thereafter for four weeks. Observers blinded to treatment groups conducted efficacy



### Efficacy against *Amblyomma americanum*



evaluations weekly.

In this study, ProMeris for dogs provided a high level of tick control through Day 28.

### Efficacy against *Amblyomma americanum* (lone star tick)

Six adult dogs were treated according to label directions with ProMeris for dogs on Day 0. Dogs were infested with ticks (*Amblyomma americanum*) on Day 7 and weekly thereafter for four weeks. Observers blinded to treatment groups conducted efficacy evaluations weekly.

In this study, ProMeris for dogs provided greater than 90 percent tick control through Day 30.

### Efficacy of four monthly treatments against *R. sanguineus* (brown dog tick)

Twelve adult dogs were treated according to label directions with ProMeris for dogs on Day 0, then retreated monthly for three months. Dogs were infested with ticks (*R. sanguineus*) 26 days after each treatment. Efficacy evaluations were conducted two days after each infestation by observers blinded to treatment groups.

In this study, ProMeris for dogs provided greater than 95 percent control of ticks through four months.

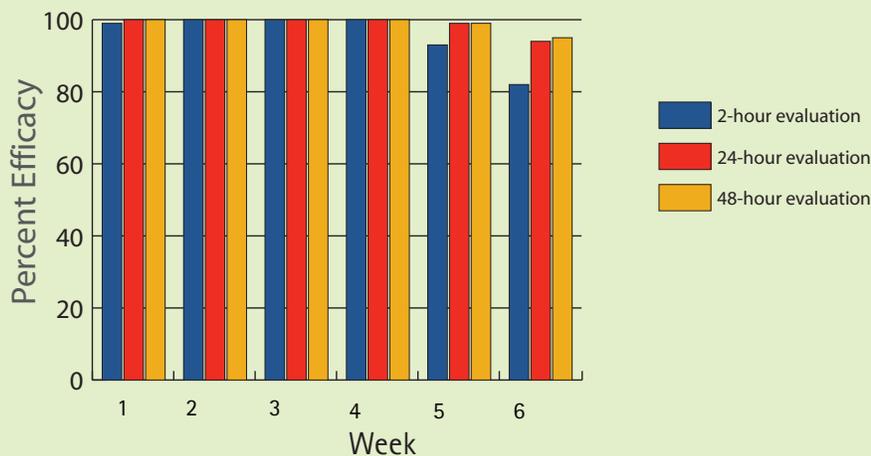
### Impact on feeding behavior of *R. sanguineus* (brown dog tick)

Eight adult dogs were treated according to label directions with ProMeris for dogs on Day 0. Dogs were infested with ticks (*R. sanguineus*) prior to each treatment, again on Day 5 and

### Efficacy of four monthly treatments against *R. sanguineus*



### Reduction in live attached ticks



then weekly thereafter for six weeks. Efficacy evaluations to determine the ability of ProMeris for dogs to prevent tick attachment were conducted 2, 24 and 48 hours after each infestation.

In this study, ProMeris for dogs provided greater than 90 percent control of tick attachment at all evaluations from Week 1 through Week 5. Based on 48-hour evaluations, ProMeris for dogs provided greater than 90 percent tick control to Week 6.

## **International Studies**

### **European field study**

A field trial was conducted in 30 veterinary practices located in France and Germany. Two hundred thirty-nine (239) healthy dogs with fleas or ticks were treated according to label directions with a single dose of ProMeris for dogs. The dogs ranged in age from 2 months to 13 years and weighed between 2 and 79 kg. A similar control group of dogs was treated with an approved flea and tick control product. After a single treatment, a veterinarian evaluated dogs approximately every other week through Day 56.

In this study, ProMeris for dogs provided effective flea and tick control through Day 56. This performance was generally similar to the other approved product. Twelve animals were reported to have adverse effects possibly related to treatment. All animals recovered. Due to problems inherent in field studies, the cause(s) of these events was not determined.

### **Australian tick field study**

*Ixodes holocyclus* (Australian paralysis tick) is a tick endemic to many parts of Australia. It is considered to be the vector of potentially fatal tick paralysis in dogs. A field study was conducted in four veterinary clinics in Australia to determine the efficacy of ProMeris for dogs against *I. holocyclus*.

Dogs were recruited for the study from locations where cases of tick paralysis had previously occurred. Twenty-seven (27) dogs were assigned to a group and treated weekly with ProMeris for dogs. A control group of 15 dogs was also recruited and treated with an approved product.

In this study, ProMeris for dogs was found to be as effective as the approved product in preventing infestation with *I. holocyclus* and preventing tick paralysis.

### **Australian flea field study**

A field trial was conducted in two locations in Australia. Fifty (50) healthy dogs with fleas were treated according to label directions with ProMeris for dogs. The dogs ranged in age from 16 weeks to 15 years and consisted of



Figures 1a. to d.

Dogs naturally infested with *Sarcoptes scabiei* mites pretreatment (Day -2) and after two treatments with ProMeris for dogs at monthly intervals (Day +56).

breeds typical of private veterinary practice. After a single treatment with ProMeris for dogs, the attending veterinarian evaluated patients at weekly intervals through Day 42.

In this study, ProMeris for dogs effectively controlled fleas at a level comparable to an approved product. After treatment, five dogs were described by their owners as experiencing events considered adverse. All observations were transitory and resolved without intervention. Due to problems inherent in the field studies, the cause(s) of these events could not be determined, but the investigators considered them not likely related to treatment.

#### Field study summary

These studies demonstrate ProMeris for dogs effectively controls fleas and ticks on dogs. ProMeris for dogs demonstrates high levels of efficacy within 24 hours and reaches maximum levels by 48 hours. ProMeris for dogs effectively controls ticks for up to four weeks and fleas for up to six weeks.

#### Data on *Sarcoptes scabiei*

Adult dogs with clinical signs of sarcoptic mange and positive skin scrapings for *Sarcoptes scabiei* were randomly placed into two treatment groups of eight



2a. Day -2



2b. Day +56



2c., Day -2



2d. Day +56

Figure 2a. to d.

Dogs naturally infested with *Sarcoptes scabiei* mites pretreatment (Day -2) and after four treatments with ProMeris for dogs at 14-day intervals (Day 56).



3a Day -1



3b Day +84



3c. Day -1



3d. Day +84

Figure 3a. to d.

Dogs naturally infested with *Demodex* mites pretreatment (Day -1) and after three treatments with ProMeris for dogs at monthly intervals (Day 84).

dogs each. One group was treated with ProMeris for dogs on Days 0 and 28. The second group was treated with ProMeris for dogs on Days 0, 14, 28 and 42. Clinical evaluations and skin scrapings from five sites were conducted on Days -2, 14, 28, 42 and 56. A clinical cure was defined as a dog having no clinical signs with two consecutive negative skin scrapings.

In this study, ProMeris for dogs demonstrated a cure rate of 75 percent in the group receiving two monthly treatments (*Figures 1a to 1d*, page 14). ProMeris for dogs demonstrated a cure rate of 83 percent in the group treated every other week (*Figures 2a to 2d*, page 15). No adverse events related to treatment were observed.

### **Data on *Demodex***

Sixteen adult dogs with clinical signs of generalized demodectic mange and skin scrapings positive for *Demodex* mites were randomly placed into two treatment groups of eight dogs each. One group was treated with ProMeris for dogs on Days 0, 28 and 56 (*Figures 3a to 3d*, page 15). The second group was treated with ProMeris for dogs on Days 0, 14, 28, 42, 56 and 70. Clinical evaluations and skin scrapings were conducted on Days -3, -2, -1, 28, 56 and 84.

In this study, seven of eight dogs in each group were considered to be free of clinical signs after treatment with ProMeris for dogs. Mite counts were reduced by 99.6 percent in the group treated every other week and 98.6 percent in the group receiving monthly treatments. Sixty-two percent of dogs in the group treated every other week were considered mite free, and 43 percent of dogs in the group receiving three monthly treatments were considered mite-free. ProMeris for dogs produced dramatic decreases in mite counts and resolved clinical signs in seven out of eight dogs treated with either protocol. No adverse events related to treatment were observed.

# Frequently Asked Questions

## *How effective is ProMeris for dogs compared with other approved products?*

ProMeris for dogs has been studied under both laboratory and field conditions to compare its activities to approved products. These laboratory and field studies indicate the performance of ProMeris for dogs to be similar to the approved products tested.

## *Will safety margins allow immediate reapplication if the owner decides the product was washed off?*

ProMeris for dogs is applied to the skin and is designed to disperse at the skin's surface and resist removal with water. Therefore, the owner would need to take considerable action to remove a significant amount of the product after its application. However, to test the response if a dog were inadvertently double-dosed, Fort Dodge conducted multiple exaggerated dose studies (up to five times the recommended dose) with ProMeris for dogs in puppies as young as 8 weeks. No clinically significant adverse responses were observed in these studies.

## *Is the product still effective if a dog jumps into a lake or swimming pool immediately after its application?*

Because ProMeris for dogs was designed to disperse quickly, patients jumping in water soon after treatment would be expected to maintain effective levels of flea and tick control. A study was conducted where dogs were treated with ProMeris for dogs on Day 0 then immersed in water on Days 2, 9, 16 and 23. While there was a slight reduction in the product's ability to control fleas and ticks, the efficacy remained at or above 90 percent through about Day 42. On Day 42, tick control was 84 percent. Therefore, patients experiencing approximately the level of water activity simulated in this study would be expected to maintain excellent levels of both flea and tick control.

## *How soon after application can a dog be bathed with shampoo without removing the product?*

In general, shampooing dogs that have been treated with topically applied flea and tick control products results in removal of some active ingredient. Therefore, it is generally recommended to minimize bathing with shampoo when using these products. A study was conducted where dogs were treated with ProMeris for dogs on Day 0 then shampooed on Day 14. Flea challenges were performed on Days 6, 13, 20, 27, 34 and 41. In the study, flea

control at 48 hours post-infestation remained above 90 percent through Day 36, while tick control was 80 percent.

### ***When is the best time to shampoo a dog treated with ProMeris for dogs?***

The best time to shampoo a dog is before, but not immediately before, its next scheduled application of ProMeris for dogs.

### ***What will happen if a dog licks ProMeris for dogs?***

Oral exposure was studied in eight adult dogs by placing approximately 10 percent of the recommended topical dose (based on the dog's weight) on the tongue. Immediately after dosing, dogs demonstrated avoidance behaviors including head shaking, licking or salivation. Within three hours of dosing, a few dogs had skin that was cool to the touch. Four dogs appeared to be lethargic. Neurologic examinations performed four hours after administration were considered normal. All animals were considered normal within 24 hours without medical intervention.

Dogs that lick ProMeris for dogs can be expected to have some salivation and lethargy. Because dogs express strong avoidance behaviors, they are unlikely to consume significant amounts of this product. If consumption of 10 percent of the dose occurs, some subtle signs of lethargy might be observed.

### ***Can ProMeris for dogs be used in breeding, pregnant or nursing dogs?***

ProMeris for dogs is not currently approved for use in these animals. Studies showed no effect on canine semen or female reproduction parameters. Additionally, treating bitches on Day 5 of lactation had no observed effect on nursing puppies. More complete studies will be conducted and submitted for regulatory review.

### ***Can ProMeris for dogs be used in geriatric dogs? Should pretreatment blood work be recommended?***

ProMeris for dogs has been used in many older dogs in field studies. In these studies, product performance was not influenced by age. Healthy older dogs, therefore, can be treated with ProMeris and no pretreatment blood work appears necessary. ProMeris for dogs has not been studied in geriatric dogs with chronic diseases. Until additional information can be collected, Fort Dodge suggests dogs of any age with chronic diseases not be treated with ProMeris for dogs.

### ***Should ProMeris for dogs be used in diabetic dogs?***

ProMeris for dogs has not been studied in diabetic animals. In mammals, amitraz can cause hyperglycemia due to alpha-2 adrenergic stimulation. The mechanism is thought to be direct inhibition of insulin release via stimulation of alpha-2 adrenergic receptors in the pancreas. It is generally advised that all alpha-2 adrenergic agonists be used with caution in diabetic animals. In exaggerated dose studies, small transitory increases (about 1.3x of baseline) in blood glucose levels were observed in normal dogs. These effects have not been seen at recommended doses. These blood glucose changes are considered clinically insignificant in normal dogs. Until additional information can be collected, Fort Dodge advises caution and close patient monitoring when using ProMeris for dogs in diabetic patients.

### ***Can dogs on separation anxiety medications be treated with ProMeris for dogs?***

Amitraz, one of the active ingredients in ProMeris for dogs, can compete with the enzyme monoamine oxidase (MAO). MAO modulates the levels of some neurotransmitters. Interaction with MAO is a common mode of action for many behavior-modifying drugs. Some of the most common MAO active drugs used in veterinary medicine are tricyclic antidepressants (*e.g.*, clomipramine). It is generally advised to use multiple MAO active drugs in the same patient with caution. The potential exists for treatment with ProMeris for dogs to affect the behavior of dogs already on MAO inhibitors. However, studies conducted on ProMeris for dogs show the amount of amitraz absorbed into the blood to be miniscule, so there is little opportunity for interaction. ProMeris for dogs has not been tested in dogs on MAO inhibitors. Until additional information can be collected, Fort Dodge suggests caution and close patient monitoring when using ProMeris for dogs in dogs taking MAO inhibitors.

### ***What types of carriers are used in ProMeris for dogs?***

The carriers of the product are the ingredients that do not kill fleas or ticks, but help the product disperse and stay on the animal. The carriers in ProMeris for dogs are not oil or alcohol based, but are considered lipophilic solvents.

### ***Can dogs treated with ProMeris for dogs be administered alpha-2 adrenergic agonists?***

Amitraz, one of the active ingredients in ProMeris for dogs, has alpha-2 adrenergic agonist properties. It is generally recommended alpha-2 adrenergic

agonists be used with caution in combination. However, studies conducted on ProMeris for dogs show the amount of amitraz absorbed into the blood to be minuscule. Amitraz levels in blood samples taken from treated dogs over several days were below the level of quantification (less than 50 nanograms/ml). Therefore, it is considered unlikely this amount of amitraz could produce significant alpha-2 adrenergic systemic effects additive with another alpha-2 adrenergic agonist. ProMeris for dogs has not been tested in dogs that have been given other alpha-2 adrenergic agonists. Until additional information can be collected, Fort Dodge advises caution and close patient monitoring when using alpha-2 adrenergic agonists in dogs treated with ProMeris for dogs.

***How do I switch a dog from another topical flea and tick control product to ProMeris for dogs?***

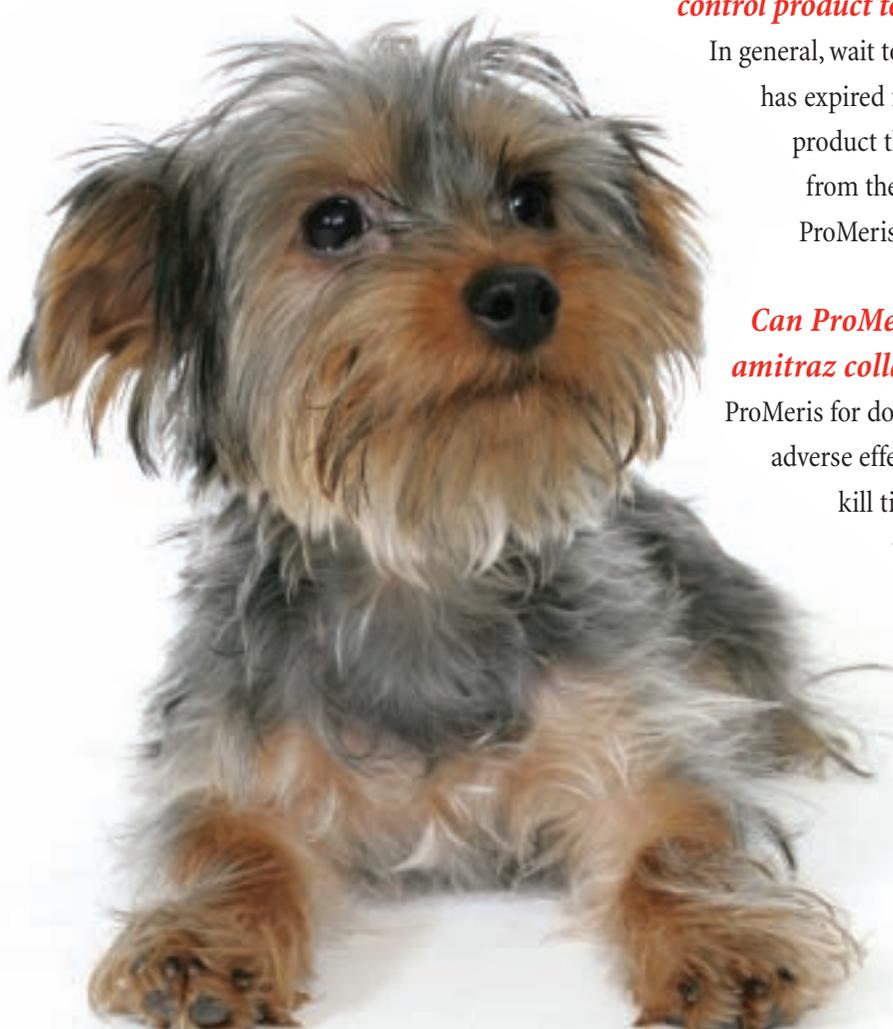
In general, wait to apply the new product until the re-application period has expired for the current product. For example, if a dog was on a product that is re-applied monthly, you would wait about 30 days from the last application of that product before applying ProMeris for dogs.

***Can ProMeris for dogs be used on dogs wearing amitraz collars?***

ProMeris for dogs has been tested on dogs wearing amitraz collars. No adverse effects were observed. Amitraz collars are commonly used to kill ticks on dogs. ProMeris for dogs also kills ticks. As these two treatments share a common active ingredient, one would not expect these collars to provide more tick control than ProMeris for dogs by itself. Dogs wearing amitraz collars can be transitioned to ProMeris for dogs by removing the collar and applying the ProMeris product.

***Can cats live in the same household as dogs treated with ProMeris for dogs?***

Yes, cats can commingle with dogs treated with ProMeris for dogs. While ProMeris for dogs should not be used on cats, it is possible cats living with treated dogs may be exposed to small amounts of ProMeris for dogs. In field trials conducted in Australia and Europe, there were



126 cats living in the same households as dogs treated with ProMeris for dogs. Because most dogs were treated twice with the product, there were a significant number of possible cat exposures. No adverse responses were observed in these cats. To study this further, six adult cats were topically administered a preliminary formulation of ProMeris for dogs consistent with their body weight (*i.e.*, a 10-pound cat was administered the volume appropriate for a 10-pound dog); this overestimates realistic exposures that may result from commingling cats with treated dogs. All cats experienced vomiting, and some appeared inappetent and lethargic. All cats recovered without intervention within 72 hours.

If you suspect a cat is suffering from adverse effects due to ProMeris for dogs, please contact Fort Dodge Professional Services at 888-PROMERIS (888-776-6374) or the ASPCA Poison Control Center at 888-426-4435. (There is a fee for ASPCA Poison Control Services.)

### ***Is amitraz toxic to cats?***

A review of the ASPCA Animal Poison Control Center database from January 2001 to March 2006 found only 13 records of suspected amitraz toxicity in cats. This was during a period when cats could have been exposed to at least two forms of amitraz used in small animal clinical practice. In those reported cases, one cat died. The quality of the data in this report did not allow determination of the dose the cat was exposed to or if the event was due to amitraz toxicity. Based on the ASPCA records, it appears high doses of amitraz can cause ataxia, hypothermia, hypotension and miosis in cats. These signs appear consistent with alpha-2 adrenergic stimulation. Treatment for amitraz exposure in cats would include removing the source and dermal decontamination. If required, physiologic support with fluids could be implemented. Body temperature should be monitored. Based on the formulation of ProMeris for dogs and its method of application it is highly unlikely cats will be exposed to significant doses of amitraz.

### ***What is the risk to people exposed to dogs recently treated with ProMeris for dogs?***

ProMeris for dogs has been designed to disperse quickly at the skin's surface, which makes accidental exposure of people less likely. Clients should follow all label directions and refrain from direct contact with the product and the application site until it has dried. If people are exposed to product liquid while treating or petting dogs, they should follow the first aid advice on the package (*e.g.*, washing hands).

### ***Are there any additional risks to diabetic people or people on MAO inhibitor therapy?***

ProMeris for dogs has an active ingredient (amitraz) that can have alpha-2 adrenergic effects in mammals. Exposure to alpha-2 adrenergics can cause increases in blood glucose and can also compete with monoamine oxidase (MAO). MAO is an enzyme that modulates some neurotransmitters, and MAO inhibition is a common mode of action for many human mood-altering drugs. Therefore, there is a potential for amitraz to impact the effects of drugs people take to manage many conditions such as anxiety. The amount of amitraz exposure required to affect a diabetic's blood glucose or to clinically impact people taking MOA drugs is not known. All clients should be advised to follow the ProMeris for dogs label directions carefully. These directions are designed to minimize human exposure to the product.

### ***What are the risks if a child were to open a container and ingest this product?***

While there is always a risk of accidental ingestion of pesticides by children, ProMeris for dogs has EPA-approved directions, which are similar to those with other commonly used flea and tick control products. Oral exposure to an entire dose of ProMeris for dogs is well below the estimated LD<sub>50</sub> for this product. The estimated mammalian oral LD<sub>50</sub> is greater than 500 mg/kg (based on amitraz). If an average 2-year-old (weight 12 kg) consumed an entire large size of ProMeris for dogs, the child would be exposed to 1,000 mg of amitraz. This can be contrasted to the estimated LD<sub>50</sub> for this weight, which is 6,000 mg. Advise anyone who consumes this product to follow all first aid directions on the package, including informing the poison control center and following all of its instructions.

### ***Does ProMeris for dogs have an odor?***

Most users of the product say ProMeris for dogs smells like eucalyptus leaves. Most of them find this odor pleasant.

### ***Will ProMeris for dogs damage flooring, carpet and furniture?***

ProMeris for dogs has been tested to determine if it will harm common objects found around the home. These studies found a negligible to slight tendency to stain lighter colors of fabric, carpet or upholstery. The product may reduce the gloss on acrylic fingernails. Clients should be advised the treatment area should not come into contact with fabrics, upholstery or carpets until it has dried.

For additional information  
about ProMeris for dogs,  
please contact a Fort Dodge  
Professional Services  
veterinarian at  
(888) PROMERIS.





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