

ProMeris™ for cats



 A technical manual for veterinarians



FORT DODGE ANIMAL HEALTH

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ProMeris for cats is a low-volume, topical spot-on designed to be applied to cats 8 weeks and older for the treatment and control of fleas. It contains the single active ingredient, metaflumizone—a semicarbazone insecticide with a novel mode of action that has shown excellent activity against fleas.

Metaflumizone

Metaflumizone is a new insecticide that has a novel mode of action as when 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 functional groups depending on where they impact 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

Metaflumizone Highlights

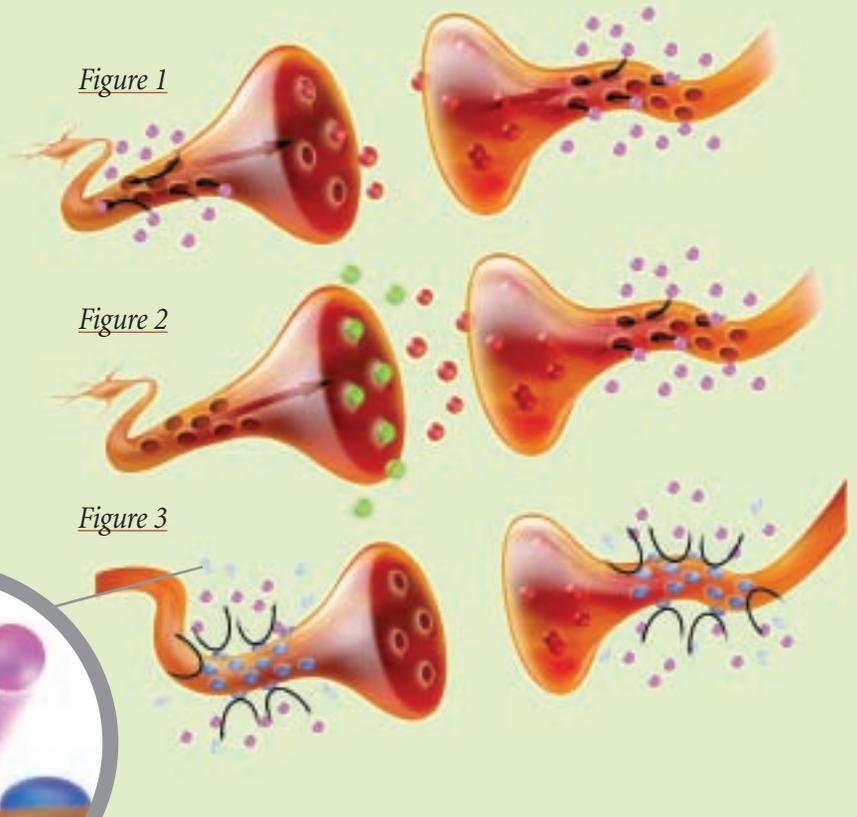
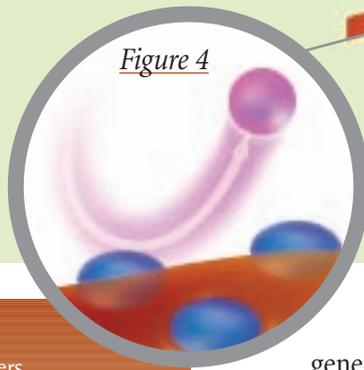
- Exhibits a novel mode of action by blocking voltage dependent sodium channels
- Controls existing flea infestations
- Protects against flea reinfestations for up to seven weeks
- Kills fleas that may cause flea allergy dermatitis
- Reduces flea egg production within 24 hours
- Approved for use on kittens 8 weeks and older
- Supported by multiple safety studies, including studies at exaggerated doses

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 dot).



Color guide

Red circles = neurotransmitters

Purple circles = sodium ions

Green circles = synaptic insecticides

Blue circles = metaflumizone

generation of the impulse (*Figure 1*).

Synaptic insecticides have many different precise actions, but their impact can be summarized as blocking or overstimulating synaptic communication. Generally, synaptic insecticides work by mimicking the neurotransmitters from the presynaptic nerve, or by blocking or changing the way the 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 that an insect's resistance to a synaptic insecticide, should it occur, would result in resistance to an axonal insecticide.*

*Ware GW, Whitacre DM. The pesticide book. Willoughby, Oh: W.H. Freeman Co: 2004;219-223.

Product Uses

ProMeris for cats can be used to control fleas on cats and kittens 8 weeks and older. It is a convenient spot-on product that provides effective control of existing flea infestations and protects against reinfestation for up to seven weeks. Monthly application is generally recommended for consistent control of fleas. ProMeris for cats can also be used to prevent flea infestation for cats taken into a flea-contaminated environment. It kills fleas effectively and thus may help to prevent and treat flea allergy dermatitis.

Packaging

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

ProMeris for cats is available in two packaging presentations for different body weights of cats or kittens 8 weeks and older. Use the small size (S) for cats under nine pounds and use the large size (L) for cats weighing nine pounds and over. Each package contains three or six individual applicator tubes for monthly treatments. Kittens 8 weeks to 6 months should be treated with the small size.

The ProMeris for cats applicator is designed to provide maximum convenience for pet owners by incorporating several features not available with some other flea 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.



Package size	Cat size (lb)
S*	Under 9
L	9 and over

*Kittens 8 weeks to 6 months should be treated with the Small size.

Pharmacokinetics

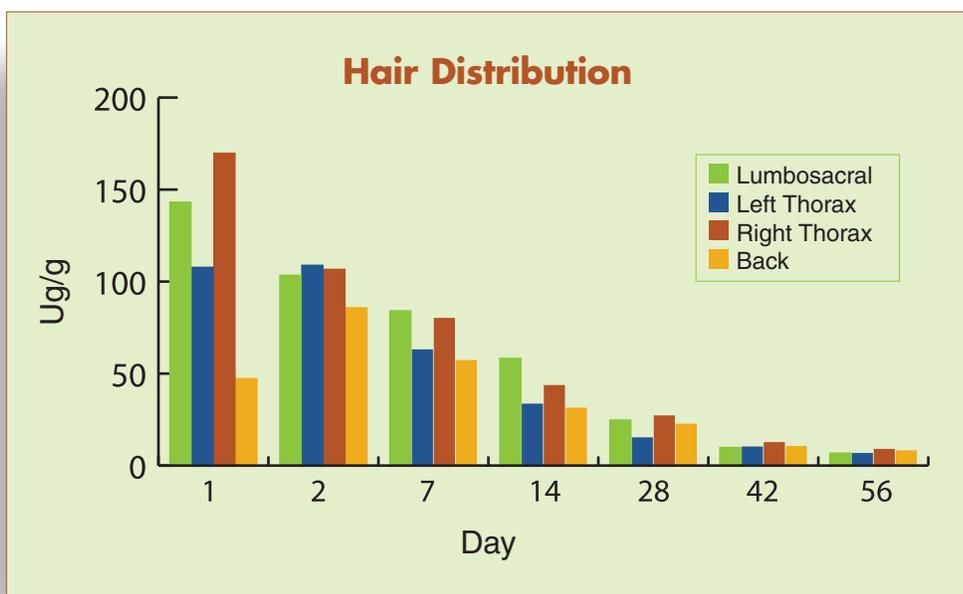
Blood levels

Researchers typically treated six adult domestic shorthaired cats with the recommended dose of ProMeris for cats. 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 metaflumizone in plasma was developed and validated. This method is able to measure drug levels greater than 50 ng/ml (ppb) of metaflumizone.

The results of the study demonstrated only very small amounts of metaflumizone are absorbed systemically from dermal application. Of all the samples taken for the duration of the study, only a single sample on a single day contained more than the limit of quantification.

Hair distribution

Six adult domestic shorthaired cats were treated according to the label recommendations with ProMeris for cats. Samples of hair were removed from the middle of the back, the lumbosacral portion of the back, and the right and left thorax on Days 1, 2, 7, 14, 28, 42 and 56. A method to measure the metaflumizone amounts in these samples was developed and validated. All sites were found to have measurable levels of metaflumizone on Day 1. These levels generally increased with peak levels found for most sites on Days 1 and 2. Levels then slowly decreased



to the end of the study. All sites had measurable levels on Day 56. These studies prove ProMeris for cats rapidly distributes on cats' skin from the site of application and has residual levels in skin and hair during its activity period.

Comparative Effects*

Active ingredient	Dermal LD ₅₀ mg/kg	Oral LD ₅₀ mg/kg
Metaflumizone	>5,000	>5,000
Imidacloprid	>5,000 ^a	450 ^a
Permethrin	>4,000 ^{a,b,c}	430 ^{a,c} to 4,000 ^{a,c}
Fipronil	>2,000 ^d	97 ^{d,e}

*LD₅₀ values are determined in standardized tests in laboratory animals. The LD₅₀ value is the dose of material resulting in death of 50 percent of the test animals. An LD₅₀ 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 LD₅₀ values imply that higher exposures are required to induce fatal toxicity. Due to differences inherent in study protocols and biological variability, small differences in LD₅₀ values may not be biologically important. These LD₅₀ values are presented to demonstrate metaflumizone has LD₅₀ 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>

K9 Advantix is a registered trademark of Bayer.

The safety profile of ProMeris for cats has been studied extensively.

Safety Studies

The safety profile of ProMeris for cats has been studied extensively. Multiple exaggerated dose studies were conducted. In these studies, the recommended dose of ProMeris for cats, three times the recommended dose or five times the recommended dose were topically administered to cats as young as 8 weeks old. In some studies, this dosing was performed once, but 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 cats. Their observations included behavior, food consumption, body weight, urinalysis, and routine hematology



Ctenocephalides felis

Male



Female



and serum chemistries. During these studies, no clinically significant adverse effects due to treatment with ProMeris for cats were observed.

In studies of mammalian toxicity, metaflumizone demonstrates low toxicity following oral exposure. There are no known mutagenic or carcinogenic effects.

The studies described demonstrate ProMeris for cats delivers the performance veterinarians demand for their patients.

Feline Efficacy Studies

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

Efficacy study design

Many studies have been conducted to determine the effectiveness of ProMeris to control and kill fleas on cats. While some specifics of the trials vary, all the presented studies share common characteristics. In all laboratory studies, healthy purpose-bred cats were randomly assigned to either a treatment group or a control group. The recommended dose of ProMeris for cats was administered to the treatment group according to label directions. The control group was given a control product (placebo) or received no treatment. A standard number of fleas (100) were placed on the cats

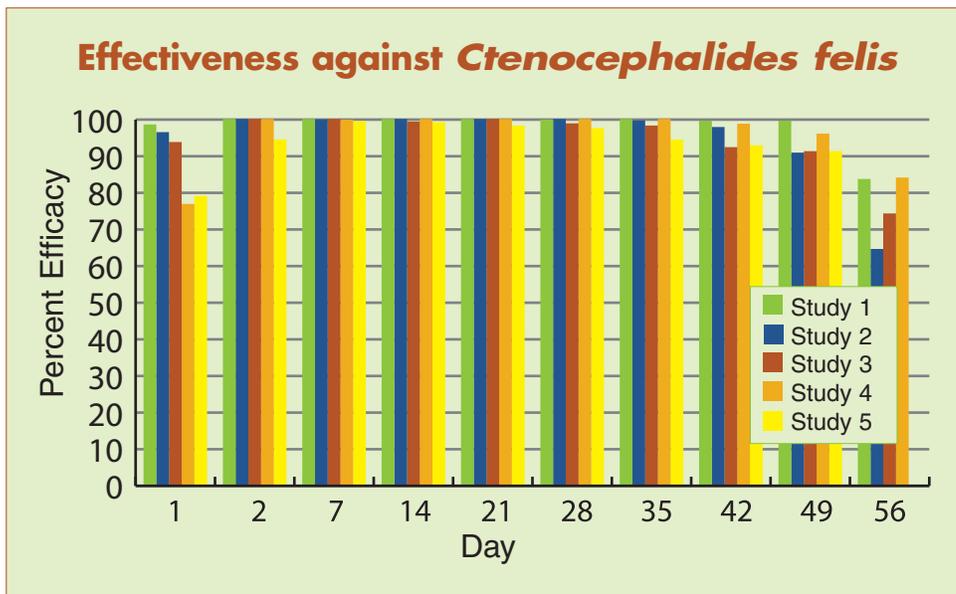
just before or after treatment; infestation was repeated weekly. Cats were inspected for flea burdens using precise standardized methods by qualified observers blinded to study groups. The initial evaluation usually occurred 24 to 48 hours after infestation and at given intervals thereafter. To determine efficacy, the number of fleas found on the nontreated control cats was compared to the number of fleas found on the cats treated with ProMeris for cats. These studies demonstrate the product effectively controls fleas on cats.



Efficacy against *Ctenocephalides felis*

Five studies were conducted with essentially identical protocols. In each study, eight adult domestic shorthaired cats were treated topically with ProMeris for cats on Day 0. Cats were infested with fleas prior to treatment, then weekly for eight weeks. Efficacy evaluations were conducted weekly until Day 56 by observers blinded to treatment groups. (One study was conducted only to Day 49.)

In all five efficacy studies, ProMeris for cats provided at least 90 percent flea control through Day 49.



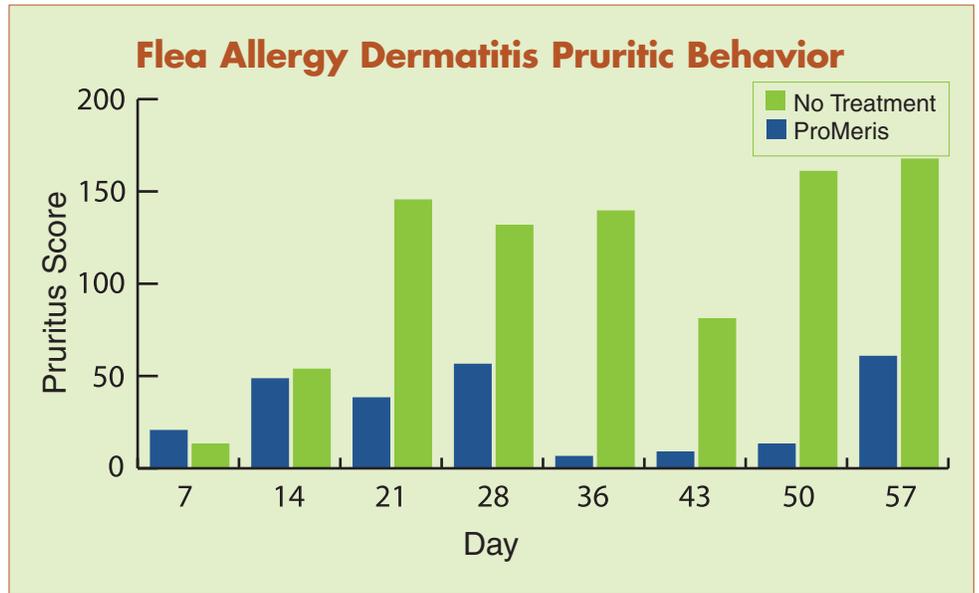
Efficacy against signs of flea allergy dermatitis

Eight adult domestic shorthaired cats with signs consistent with flea allergy dermatitis were treated as recommended with ProMeris for cats on Days 0 and 30. Cats were infested with fleas and evaluated on Days 1 and 4, and then weekly for seven weeks by observers blinded to the treatment groups. The observers looked for flea infestations, signs of pruritus and skin lesions. Pruritic behavior was recorded. Signs of skin disease (erythema and skin lesions) were converted to a numeric score. Fleas were not removed during these evaluations.

In this study, cats treated with ProMeris for cats had pruritic behavior scores consistently below nontreated controls from Day 14 through the end of the trial. These reductions ranged from 57 to 95 percent from Day 21 to the end of the trial. The differences in these scores were statistically



significant ($P < 0.05$) on Days 36 through 57. Skin lesions showed similar reductions ranging from 60 to 100 percent. Due to high variability in the skin lesion scores, these reductions were not statistically significant.



Efficacy against adult fleas and flea egg production

Eight adult domestic shorthaired cats were treated with ProMeris for cats on Day 0. Cats were infested with fleas two days prior to treatment, and then weekly, following treatment, for eight weeks. Efficacy evaluations



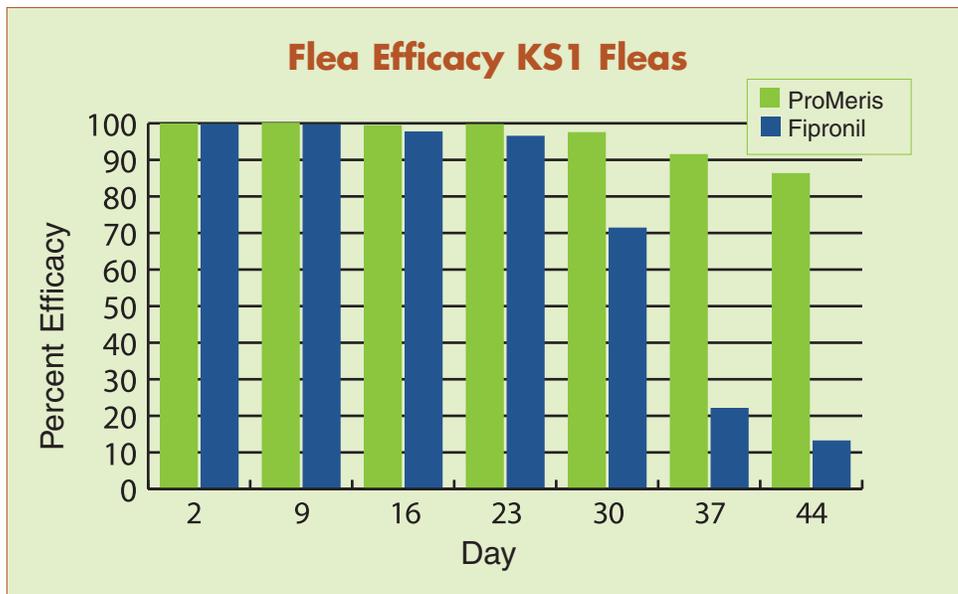
were conducted weekly by observers blinded to the treatment groups.

In this study, ProMeris for cats demonstrated greater than 99 percent efficacy on all evaluations of adult fleas through Day 45 and greater than 90 percent efficacy through Day 52. The product demonstrated greater than 99 percent efficacy to control flea egg production from Day 2 through 38 and greater than 95 percent efficacy through Day 45.

This study demonstrated ProMeris for cats confers rapid and consistent control of adult fleas and flea egg production. As adult female fleas must feed on animals to produce eggs, this dramatic reduction in flea egg production suggests ProMeris for cats is effective at rapidly reducing flea feeding.

Efficacy against the KS1 strain of fleas

Twenty-four adult domestic shorthaired cats were randomly divided into three groups of eight. On Day 0, Group 1 was treated with the minimum recommended dose of ProMeris for cats, Group 2 was treated at the minimum recommended dose with an approved flea control product



*Fipronil has been shown to have reduced persistency of control for KS1 fleas as compared to other fleas. [Payne PA, Dryden MW, Smith V, et al. Effect of 0.2% w/w fipronil spray on adult flea mortality and egg production of three different cat flea, *Ctenocephalides felis* (Bouche), strains infesting cats. *Vet Parasitol* 2001;102:331-340.] The KS1 strain of fleas has also been shown to have the Rdl resistance genetic mutation. [Bass C, Schroeder I, Turberg A, et al. Identification of the Rdl mutation in laboratory and field strains of the cat flea *Ctenocephalides felis* (Siphonaptera: Pulicidae). *Pest Manag Sci* 2004;60:1157-1162.]



containing fipronil, and Group 3 was not treated. Cats were infested with the KS1* strain of fleas and blinded observers evaluated them weekly.

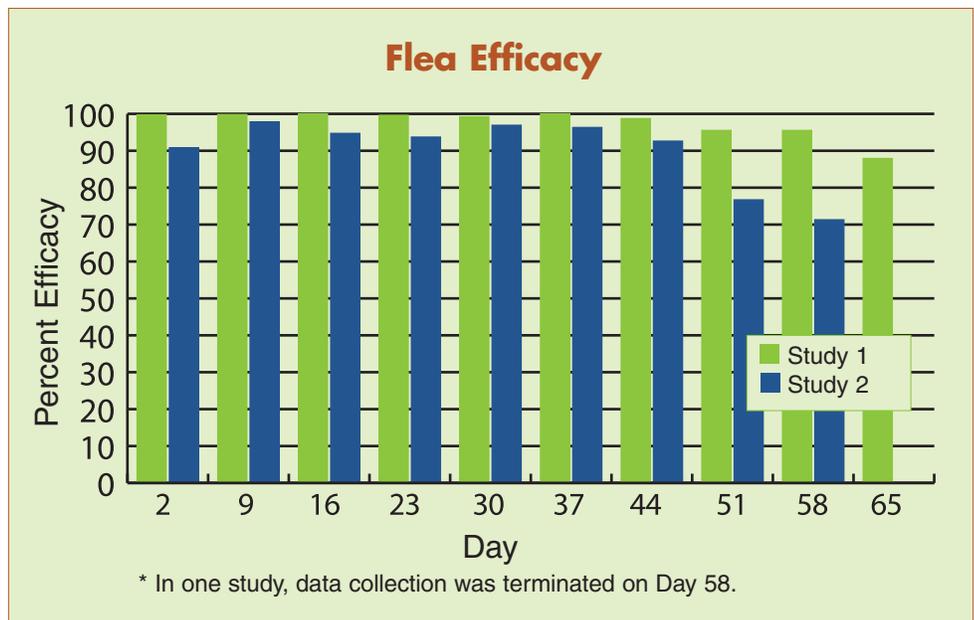
In this study, ProMeris for cats demonstrated greater than 95 percent efficacy against fleas through Day 30. In contrast, the product containing fipronil demonstrated greater than 95 percent efficacy against fleas only through Day 23 and dropped to 71 percent effectiveness on Day 30. The differences in efficacy between the treatment groups were statistically significant ($P < 0.05$) from Day 23 through the end of the study.

These results suggest ProMeris for cats has activity against fleas with reduced susceptibility to fipronil.

International Studies

In each of two European studies, eight adult domestic shorthaired cats were treated with the recommended dose of ProMeris for cats on Day 0. Cats were then infested with fleas and evaluated weekly by observers blinded to the treatment groups.

In these studies, ProMeris for cats provided greater than 95 percent flea control through Day 37 and Day 58.



European field study

A field trial was conducted in 24 clinics in France and Germany. Ranging in age from 3 months to 16 years, 294 healthy cats with fleas were recruited for the study. From these healthy cats, 188 were randomly

placed in a group treated with ProMeris for cats and as a control group, 106 cats were treated with an approved flea control product. After a single treatment, cats were evaluated for product efficacy on Days 14, 28, 42 and 56 by veterinarians blinded to treatment groupings.

In this study, ProMeris for cats provided greater than 90 percent efficacy through the end of the study (efficacy on Day 28 was 89.4 percent). This level of efficacy was similar to the approved product. One cat was observed with transient lethargy after treatment. Four cats had mild cosmetic alterations of the treatment site considered likely to be a result of the treatment. All abnormalities resolved without medical intervention.

Summary of Efficacy Study Results

ProMeris for cats begins killing quickly with high levels of efficacy more commonly seen at 24 hours. It rapidly reduces flea egg production to very low levels within 24 hours. This effect is seen consistently with repeat infestations. ProMeris for cats consistently shows effectiveness for at least one month and can last for up to seven weeks, allowing it to fit easily into a monthly flea control regimen.



Frequently Asked Questions

How effective is ProMeris for cats when compared with other approved products?

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

How rapidly does ProMeris for cats work on reducing flea egg numbers?

ProMeris for cats has been shown to dramatically kill adult fleas and to essentially stop their ability to produce eggs. Our research indicates that by two days following treatment with ProMeris, flea egg production has been reduced by more than 99 percent. This level of reduction is consistently seen for more than a month. As mature female fleas must feed to produce eggs, these data suggest ProMeris for cats is very effective at reducing flea feeding. This activity interrupts the life cycle of the flea.

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

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

What will the treatment site look like?

Hair at the treatment site may look wet or unruly for a day or so. This appearance is similar to treatment sites from other monthly spot-on treatments.

What happens if cats lick this product?

If applied correctly, cats won't be exposed to this product orally. In a study, eight cats about 6 months old were intentionally administered approximately 10 percent of the recommended topical dose orally. The cats demonstrated immediate avoidance behaviors (e.g., head shaking and salivation), confirming accidental oral exposure is unlikely. All clinical signs resolved within 45 minutes without medical intervention. Oral administration of 10 percent of the recommended dose had no effect on body weight, food consumption, neurological examinations or clinical pathology parameters.

Can ProMeris for cats be used in breeding, pregnant or nursing animals?

ProMeris for cats is not currently approved for use in these animals. A pilot study found ProMeris for cats had no impact on female reproduction or on kittens nursing treated queens. A more complete study will be conducted and submitted for regulatory review.



Should ProMeris for cats be used in geriatric cats? Should pretreatment blood work be recommended?

ProMeris for cats has been used in many older cats in field studies. In these cases, product safety was not influenced by age. Healthy older cats, therefore, can be treated and no pretreatment blood work appears necessary.

ProMeris for cats has not been studied in geriatric cats with chronic diseases. Until additional information can be collected, Fort Dodge suggests geriatric cats with chronic diseases be treated with caution.

What is the risk to people exposed to cats recently treated with ProMeris for cats?

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

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

ProMeris for cats is supplied in child-resistant packaging. Oral exposure to an entire dose of ProMeris for cats is well below the estimated LD₅₀ for this product. The estimated mammalian oral LD₅₀ is greater than or equal to 5000 mg/kg. If an average 2-year-old (weight 12 kg) consumed an entire large size of ProMeris for cats, the child would be exposed to 320 mg of metaflumizone. This can be contrasted to the LD₅₀ for this weight estimated at 60,000 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 its instructions.

Will ProMeris for cats damage flooring, carpet and furniture?

ProMeris for cats 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 on ProMeris for cats, please contact a Fort Dodge professional services veterinarian at (800) 533-8536.



