ABSTRACT

The topical endectocide selamectin (Revolution™, Pfizer Animal Health) was evaluated in seven veterinary dermatology specialty clinics for its ability to control fleas on 75 dogs and 46 cats from single- and multiple-animal households. All animals were treated on days 0, 30, and 60 with a minimum unit dose of 6 mg/kg of selamectin applied to the skin in a single spot at the base of the neck in front of the scapulae. The product was applied according to label instructions, and the use of other topical or environmental flea control products was prohibited during the study. Efficacy was assessed by percentage reductions in geometric mean flea comb counts. The reductions in flea numbers for dogs and cats combined were 90.6%, 97.0%, and 98.0% on days 30, 60, and 90, respectively, compared with day 0. This study demonstrates that selamectin, applied at 30-day intervals to dogs and cats, effectively controls flea infestations without other flea control products in single- and multiple-animal households.
INTRODUCTION
The semi-synthetic avermectin, selamectin, became commercially available to veterinarians in the United States during the fall of 1999. Avermectins selectively induce neuromuscular paralysis of target organisms by increasing chloride permeability and by targeting glutamate-gated chloride channels.\(^1\) The influx of chloride ions that follows inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods. The net effect is a rapid flaccid paralysis that leads to death or elimination of the parasite from the host. Studies conducted in support of compound registration showed that selamectin had broad-spectrum activity against fleas (Ctenocephalides felis), heartworm (Dirofilaria immitis) larvae, and ear mites (Otodectes cynotis) in dogs and cats; sarcoptic mange mites (Sarcoptes scabiei) and the American dog tick (Dermacentor variabilis) in dogs; and hookworms (Ancylostoma tubaeforme) and roundworms (Toxocara cati) in cats.\(^2\)–12

The efficacy profile of selamectin against fleas on dogs and cats was first elucidated in a series of controlled laboratory studies. Selamectin killed \(>98\%\) of adult fleas within 24 to 36 hours of topical application,\(^3\),4 and the lethal effect persisted against reinfesting fleas for approximately 30 days.\(^9\) Additional laboratory studies established that a single topical administration of selamectin was effective for 30 days in killing flea eggs and in reducing maturation of eggs to larvae and larvae to adults.\(^4\) Subsequent clinical trials showed that dogs and cats treated with selamectin, including those with pre-existing flea allergy dermatitis, had improvements in clinical signs associated with fleas as a direct result of eliminating fleas from the animals and their environment.\(^9\) The purpose of the study reported here was to further assess the efficacy of selamectin against natural flea infestations on dogs and cats presented as patients to veterinary dermatology specialty clinics.

MATERIALS AND METHODS

Animals
Seven veterinary dermatology specialty clinics located in various geographic areas of the United States participated in the study. Privately owned male, female, male neutered, and female neutered dogs and cats of various breeds and crossbreeds presented as patients to the clinics were eligible for entry. Animals selected for enrollment were maintained in their normal domestic environments, with or without other animals, and were fed their usual diets. Medical management during the trial followed the standard procedures of each clinic.

All dogs and cats within a household were enrolled in the study when that household was selected for inclusion. A minimum of one animal from each household needed to be infested with \(\geq 15\) fleas after an initial flea counting before enrollment of the household.

Exclusion Criteria
Animals were excluded from participation in the study if they:

1) were younger than 6 weeks
2) had a history of apparent reactions to topical products, avermectins, or milbemycins
3) were treated with an avermectin or milbemycin in the preceding 30 days, other than those approved for heartworm prophylaxis that were used in accordance with label recommendations
4) were treated within the preceding 30 days with long-acting flea control products such as lufenuron, imidacloprid, fipronil (dogs and cats), or in the preceding 6 months with injectable lufenuron (cats)
5) had skin lesions at the site of drug application
6) were debilitated or had a history of a serious medical condition such as terminal cancer, renal failure, or unregulated medical conditions (e.g., unregulated Cushing’s or thyroid disease). The decision on whether to enroll an animal with a pre-existing medical condition was left to the discretion of the investigators.

Animals scheduled for routine surgical procedures (e.g., ovariohysterectomy, castration, or dental prophylaxis) were allowed to participate. It was recommended that selamectin be used with caution in underweight animals, but there were no weight restrictions. It was also recommended that dogs 6 months or older be tested for the presence of adult heartworm (D. immitis) antigen and circulating microfilariae within the preceding year; however, it was not a requirement that animals be heartworm negative to be enrolled in the study. Owners were advised of the nature of the study and signed an informed consent agreement before their animals’ inclusion.

 Procedures and Study Design

Study day 0 was defined as the day on which the first animal in each household was first treated with selamectin. All dogs and cats in multiple-animal households had to be enrolled on day 0 or within 9 days after treatment of the first animal enrolled from the household. Subsequent treatments, assessments, or other procedures were to be completed within 9 days before or 9 days after established due dates (within 19 days). Eligible animals received a physical examination on day 0 or within 9 days after day 0, and their medical histories were recorded.

Flea infestations were assessed according to the number of live adult fleas detected during a flea comb count procedure. The animal was manually restrained and the entire coat was combed with a flea comb for a minimum of 5 minutes with firm pressure on each stroke to ensure removal of fleas on the skin. Fleas were counted and were not replaced on the animal. After the first 5 minutes, the procedure was continued in 1-minute increments (if any fleas were removed during the preceding minute of combing) until no fleas were removed or until 30 minutes had elapsed.

Table 1 summarizes the study design. Each animal was weighed before treatment on days 0, 30, and 60, and the flea infestation was assessed in accordance with the comb count procedure. All dogs and cats received a minimum unit dose of 6 mg/kg selamectin in the commercial formulation. The pet owner, an authorized agent, or a member of the veterinary practice staff administered selamectin at the veterinary clinic according to the following procedure:

1) Any foreign material adhering to the administration site was removed before application.
2) Care was taken to ensure that the administration site was dry.

<table>
<thead>
<tr>
<th>TABLE 1. Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Selamectin</td>
</tr>
</tbody>
</table>

*Unit dosing
3) The hair was parted to ensure direct application to the skin.
4) The treatment was administered at a single site to the skin of each animal’s back, at the base of the neck anterior to the scapulae, by slowly emptying the applicator(s).
5) Treatment details were recorded.
6) Animals were not groomed, washed, or allowed to swim for 2 hours after selamectin administration.

Flea comb counts were made by a veterinarian or other qualified personnel on days 0, 30, 60, and 90, and clinical observations were made by a veterinarian on the same days. Flea assessments on each of the treatment days were conducted before the administration of selamectin.

No compound with antiparasitic activity, other than selamectin, was used during the study, with the exception of pyrantel, oxantel, and praziquantel for treatment of gastrointestinal nematodes and avermectins and milbemycins approved for heartworm prophylaxis at the label-approved dose and regimen. All treatments and medicaments (including vitamin, mineral, or essential fatty acid supplements, vaccines, anthelmintics, or agents for heartworm prophylaxis) were recorded on the animal’s veterinary report form.

Owners were informed that use of medicated shampoos (e.g., flea shampoo) was not permitted during the time the household was enrolled in the study. Use of flea combs except by, or under the supervision of, a participating veterinarian at the specified evaluation dates was not permitted. Clients also were instructed to administer only veterinarian-approved medicaments, all of which were recorded on the animal’s veterinary report form.

All animals in a household had to remain in the trial through day 90 for the household to complete the study. Withdrawal of any animal from a household that occurred before the day-90 completion date necessitated exclusion of the animal and full documentation of the reason for removal. A household was allowed to continue in the study if an animal was permanently removed from the household.

**ANALYSIS**

Only data from households in which one animal had at least 15 fleas on study day 0 were analyzed. Flea counts also were assessed within 9 days before or after days 30, 60, and 90 for each animal and were recorded as counts for days 30, 60, and 90. A general linear repeated measures mixed model that included a fixed effect for day of study was used to analyze the natural log transformed flea counts. One degree of freedom contrasts were made for each day of study versus day 0 after detection of a significant \( P \leq .05 \) day of study effect. Flea counts were transformed by the natural log \((\text{count} + 1)\) before analysis, and after analysis the least squares means were back-transformed to geometric means for presentation. Arithmetic mean flea counts also were calculated on days 0, 30, 60, and 90. Differences in mean flea counts at days 30, 60, and 90 compared with day 0 were considered statistically significant when \( P \leq .05 \). All analyses were performed using SAS software.

Percentage of reduction of the flea counts was calculated with the arithmetic mean flea counts and with the geometric mean flea counts using the following formula in which day \( i \) represents day 30, 60, and 90:

\[
100 \times \left( \frac{\text{mean count at day 0} - \text{mean count on day } i}{\text{mean count at day 0}} \right)
\]

Both the analysis and the estimates of percentage of reduction were done for dogs and cats separately and for both species combined.
RESULTS

Animals

A total of 121 animals (46 cats and 75 dogs) presented as patients to seven clinics specializing in veterinary dermatology were enrolled in the study from July 19, 1999, to January 28, 2000. The patient population was recruited from various geographic regions of the United States (e.g., California, Florida, Ohio, Texas, and Virginia) and included 13 breeds of cats and 41 breeds of dogs. There were 24 female and 22 male cats and 40 female and 35 male dogs. The animals ranged in age from 7 weeks to 14 years (median: cats = 5.0 years, dogs = 3.0 years) and in weight from 0.7 to 49.1 kg (median: cats = 4.0 kg, dogs = 19.0 kg) on trial day 0. Sixty-eight of the 121 animals lived indoors, 28 lived outdoors, and 25 lived both indoors and outdoors.

Households

Thirty-five households participated in the study (Table 2). One household with two animals enrolled did not complete the study because of an apparent adverse event in one of the animals (see the following Health Observations section for details). Four animals from another household did not complete the study, and another two animals from two separate households did not complete the study. Of these eight animals (excluding the two from the adverse-event household), four were sold and permanently removed from the household, one was given away, and one ran away.

Health Observations

No severe adverse drug reactions or mortalities occurred during the study. Seventeen cats (37.0%) and 45 dogs (60.0%) received other therapeutic or prophylactic medication during the study period in which selamectin was administered.

Nine cats (19.6%) and 25 dogs (33.3%) had histories of recent or recurrent medical conditions. Pre-existing medical conditions observed in animals enrolled in the study included asthma, alopecia, abscess, crusts, conjunctivitis, collapsed trachea, cataracts, cyst, diarrhea, demodicosis, erythema, ear mites, flea allergy dermatitis, gastrointestinal tract infection, glaucoma, heart murmur, hypothyroidism, inflammatory bowel disease, lick granuloma, papules, pruritus, pregnancy, polydipsia, polyuria, otitis, seborrhea, seizures, urinary incontinence, and vomiting. Two dogs were positive for microfilaria and adult heartworm antigen when tested for heartworm disease before the beginning of the study. No adverse events were observed in these animals.

In this study an adverse drug event was defined as any abnormal clinical sign that occurred while the dog was receiving selamectin, without regard to causality (i.e., whether or not the event was directly attributable to drug administration). Possible adverse events were reported in 20 animals during this study, with a total of 25 individual clinical signs reported (Table 3).

Of these signs, reports of alopecia in two cats
had the highest suspicion of being drug-related events. In one reported adverse event, alopecia at the treatment site, crusts on the dorsum of the neck, and foamy vomiting occurred in one animal 6 days after treatment with selamectin. Results of a complete blood count and serum biochemical profile completed 7 days after treatment were normal. This household, which included two animals, was removed from the study at the owner’s request. In another report,
alopecia was noted at the treatment site after the day-0 dosing. Hair regrew in the month after application, and the alopecia did not recur after subsequent treatments. None of the remaining signs were determined to be related to treatment (Table 3).

Efficacy

Geometric and arithmetic means and percentages of reduction in fleas were calculated for all 35 households participating in the study and for the separate populations of dogs and cats (Table 4). The reductions in flea numbers for dogs and cats combined were 90.6%, 97.0%, and 98.0% on days 30, 60, and 90, respectively, compared with day 0. These reductions in flea counts were significant at days 30, 60, and 90, compared with day 0. Data from the one household that did not complete the study were included in the analysis until the household was withdrawn.

**DISCUSSION**

Efficacy of the recently introduced companion-animal endectocide selamectin against fleas on dogs and cats was initially demonstrated in a series of controlled prelicensing laboratory and field studies. The study reported here was conducted to further define the efficacy of selamectin in the treatment and control of natural flea infestations of dogs and cats presented to veterinary dermatology specialists throughout various geographic regions of the United States.

Animals recruited for the study came from diverse household backgrounds and included pure and mixed breeds, varying widely in age, weight, and general health status. The majori-

---

**TABLE 4. Flea Counts—Geometric and Arithmetic Means and Percentages of Reduction**

<table>
<thead>
<tr>
<th>Day of Study</th>
<th>Geometric Mean Percentages of Reduction</th>
<th>Arithmetic Mean Percentages of Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Mean</td>
<td>Arithmetic Mean</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14.8*</td>
<td>35.4</td>
</tr>
<tr>
<td>30</td>
<td>1.4†</td>
<td>90.6</td>
</tr>
<tr>
<td>60</td>
<td>0.5†</td>
<td>97.0</td>
</tr>
<tr>
<td>90</td>
<td>0.3†</td>
<td>98.0</td>
</tr>
<tr>
<td>Cats:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8.1*</td>
<td>29.1</td>
</tr>
<tr>
<td>30</td>
<td>0.6†</td>
<td>92.3</td>
</tr>
<tr>
<td>60</td>
<td>0.3†</td>
<td>96.1</td>
</tr>
<tr>
<td>90</td>
<td>0.2†</td>
<td>97.7</td>
</tr>
<tr>
<td>Dogs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18.0</td>
<td>39.2</td>
</tr>
<tr>
<td>30</td>
<td>1.7†</td>
<td>90.8</td>
</tr>
<tr>
<td>60</td>
<td>0.4†</td>
<td>97.9</td>
</tr>
<tr>
<td>90</td>
<td>0.2†</td>
<td>99.1</td>
</tr>
</tbody>
</table>

*Mean less than 15 because only one animal in multiple-animal households was required to have 15 or more fleas.
†Significantly ($P \leq .05$) different from day 0.
ty (56.2%) lived indoors, 20.7% lived both indoors and outdoors, and the remaining 23.1% lived outdoors. Six of the seven dermatologists who participated in the study practice in geographic regions where fleas remain viable all year. A minimum of one enrolled animal in each household began the study infested with at least 15 adult fleas, and the arithmetic mean number of fleas present per animal on day 0 was 35.4. This would constitute a heavy infestation of fleas in the population.

Selamectin applied topically at the label-recommended dosage for 3 months reduced the geometric mean number of viable fleas on the naturally infested dogs and cats from 14.8 on day 0 to 0.3 on day 90. There was a 98.0% reduction in flea counts on the treated animals 90 days after the first treatment. Such performance is noteworthy for several reasons. First, the study protocol limited flea control measures to the administration of selamectin alone. No supplementary control practices were implemented to protect dogs and cats against new generations of fleas that might emerge from pupae harbored in household microenvironments. Second, 93.4% of the animals were from multiple-animal households, in which it is generally more difficult to control flea infestations. Third, the flea counting procedure was thorough and quantitative. Flea comb counts were performed on all areas of the body for up to 30 minutes. This procedure ensured that no fleas were missed versus methods that employ only visual estimates of flea numbers.

The current trial corroborates the findings of pivotal prelicensing flea efficacy studies. Selamectin in those trials reduced flea comb counts by >99% after 3 monthly treatments by means of its adulticidal, ovicidal, and larvicidal activity. The combined effects over 90 days interrupted the flea breeding cycle, reducing and eventually eliminating residual flea populations in the household environment. Data from the prelicensing studies and the current field study indicate that monthly topical application of selamectin at the label-recommended dose is effective in the long-term treatment and control of flea infestations on dogs and cats, even in household environments where conditions may be favorable to the propagation of successive reinfections.

The results of this study further confirm the safety of selamectin in dogs and cats. Only two cats (1.7% of the study population) developed problems that the veterinarians attributed to selamectin. Eight Australian Shepherds, two Australian Shepherd crosses, and one Collie cross were treated. These breeds may be sensitive to the effects of some avermectin compounds at dosages used for control of ectoparasites. The age of animals ranged from as low as 7 weeks to as high as 14 years. Some patients had pre-existing medical conditions including asthma, glaucoma, cataracts, hypothyroidism, inflammatory bowel disease, and seizures. Two dogs were positive for microfilaria and adult heartworm antigen. Two dogs, an Australian Shepherd and a Bulldog, and one cat were pregnant and gave birth during the study. The puppies were treated when they were 7 weeks old. None of these animals experienced adverse events attributable to treatment with selamectin.

CONCLUSION

The topical application of selamectin (Revolution™) at monthly intervals as a unit dose providing the recommended minimum of 6 mg/kg was safe and highly effective against natural infestations of fleas on dogs and cats presented to veterinary dermatology specialists in various geographic locations in the United States. At 90 days after the initial treatment, there was a 98% reduction in flea counts of dogs and cats treated monthly with selamectin.
and maintained in households where no environmental control measures were implemented. Thus, the results of this study indicate that the use of selamectin alone is likely to be a very effective method of flea treatment and control because it not only removes fleas from the pet but also may reduce the residual population in the household environment.

REFERENCES