

# Efficacy of Imidacloprid on Dogs and Cats with Natural Infestations of Fleas, with Special Emphasis on Flea Hypersensitivity\*

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## ■ ABSTRACT

In this study the efficacy of a 10% weight per volume solution of imidacloprid—registered as a flea control agent with the trademark Advantage<sup>®</sup> topical solution—was assessed in Italy under field conditions in a total of 3272 dogs and cats. During the 4-week trial the number of fleas on each animal was assessed and lesions of flea allergy dermatitis (FAD; i.e., miliary or maculopapular dermatitis, hyperpigmentation, and crusty thickenings of the skin), alopecia, and pruritus were evaluated. Imidacloprid had a notable adulticidal effect and residual activity that controlled fleas and prevented reinfestation of treated animals for at least 4 weeks. In addition, a significant decrease of the clinical signs was documented regardless of each animal's breed, sex, body size, \*This study was sponsored by Bayer S.p.A., Italy.

haircoat length, and living conditions. Some of the dogs were washed or shampooed after treatment without showing statistical differences in efficacy. This study demonstrates that a single treatment with imidacloprid is able to effectively control flea infestations in dogs and cats for at least 28 days and significantly contributes to the improvement or disappearance of clinical signs of FAD.

## ■ INTRODUCTION

Flea infestations—well known for causing discomfort in dogs and cats—are often associated with variable degrees of clinical signs such as itching, alopecia, miliary or maculopapular dermatitis, hyperpigmentation, and crusty thickenings of the skin that are suggestive of FAD, which is also often referred to as flea hypersensitivity. Fleas act as vectors for various diseases and

are significant carriers of tapeworms (*Dipylidium caninum*). Flea reproduction generally occurs in the animal's bedding as well as the environment.<sup>1,2</sup> In recent years various efforts have been made to develop new agents for flea control. Besides insecticides that act against adult fleas, there are two types of so-called insect growth regulators: one is a juvenile hormone analogue<sup>3-7</sup> and the other is a systemic chitin synthesis inhibitor.<sup>8-10</sup> However, these compounds are only effective in preventing viable flea reproduction and development. Elimination of existing flea burdens on animals must be accomplished with an adulticidal insecticide. Imidacloprid has a proven potential as a flea control agent.<sup>11-13</sup> It belongs to the chloronicotinyl nitroguanidine insecticides, a new subgroup of heterocyclic nitromethylenes.<sup>14</sup> The mode of action of imidacloprid is through depolarization of nicotinic receptors in the postsynaptic region of the insect nerve.<sup>15</sup> Its favorable mammalian safety characteristics, rapid therapeutic effect, and long-term prophylactic protection have been demonstrated in several studies.<sup>11-13,16</sup>

The objectives of the study reported here were (1) to assess the efficacy of imidacloprid on natural flea infestations in dogs and cats; (2) to determine the therapeutic effect on clinical signs and symptoms of FAD, such as itching (pruritus) and associated alopecia; (3) to test whether sex, breed, body size, haircoat length, housing conditions, and washing (dogs only) have any significant influence on the flea control efficacy of the product; (4) to confirm the safety of the product.

## ■ MATERIALS AND METHODS

### Trial Monitoring and Schedule

The study was conducted in Italy by veterinary investigators in 423 clinics. The trial started on the treatment day (day 0). Before treatment all animals underwent a clinical examination to estimate the number of existing

fleas and degree of clinical signs. Counting was performed with the animal in an upright position on all four legs by stroking the animal's back and neck against the lie of hair as well as by recording the approximate number of fleas around the ears. This procedure was repeated on both flanks. The abdomen, the inner part of the thighs, the armpits, the ventral region of the neck, and the chin were examined while keeping the animal standing upright on the rear legs or on its back. The evaluation of flea infestation was repeated in the same manner on days 1, 14, 21, and 28. The infestation was scored 0 for no fleas, 1 for  $\leq 5$  fleas (mild infestation), 2 for  $>5 < 20$  fleas (moderate infestation), and 3 for  $>20$  fleas (heavy infestation). The efficacy was calculated on the basis of the average score value reduction at the different times of the trial with respect to the pretreatment average score. During the first examination of the animals, one or more flea specimens were collected by the veterinarians in order to identify the flea species present on dogs and cats within the domestic environment.

In addition, itching and alopecia were ranked 0 for absent, 1 for rare or mild, 2 for frequent or moderate, and 3 for continuous or severe. FAD was evaluated according to the severity of miliary or maculopapular dermatitis, hyperpigmentation, and crusty thickenings of the skin and ranked 0 for absent, 1 for mild, 2 for moderate, and 3 for severe. The dermal safety of the product was assessed at each examination by considering the presence or absence of haircoat discoloration, alopecia, erythema, and hyperkeratosis at the site of application. In addition, every other general symptom, adverse event, or side effect that occurred during the study was reported.

### Animals

Each dog or cat older than 8 weeks that had more than three fleas at the primary examination

was admitted to the study. No exceptions were made regarding breed, sex, body size, or housing conditions. The total number of privately owned animals included in this study was 3272, consisting of 1939 dogs and 1333 cats. The ratio of males to females was approximately 1:1 (1634 male and 1638 female) for both dogs and cats. Most animals were middle-aged ( $>1$  and  $\leq 7$  years); 19% of dogs and cats were younger than 1 year. Animals treated with insecticides within 60 days before admission were excluded from the trial. Owners were requested not to wash their animals during the 28-day trial.

### Treatments

Advantage® (Bayer-AG Animal Health) is an odorless, 10% weight per volume, topical solution of imidacloprid for veterinary use. The product was dispensed in spot-on, ready-to-use, single-dose pipettes containing 0.4 mL, 0.8 mL, 1.0 mL, or 2.5 mL. All animals that met the inclusion criteria received a single administration at the beginning of the study (day 0). Dogs were administered one 0.4-mL pipette for animals 1 to 4 kg in weight, one 1.0-mL pipette for 4 to 10 kg, and one 2.5-mL pipette for 10 to 25 kg, applied between the shoulder blades. In dogs with weights between 25 and 50 kg, a second 2.5-mL pipette was applied on the lumbar region. Cats between 1 and 4 kg received one 0.4-mL pipette and cats over 4 kg received one 0.8-mL pipette, applied on the neck at the cranial base. No insecticidal treatment was allowed in the environment of the animals during the trial. Dogs and cats living with other animals (dogs and/or cats; multiple-animal households) as well as dogs and cats living without other animals (single-animal households) were treated. Only the animals brought to the veterinarian were treated with imidacloprid. Other animals from the same households as the study subjects were not examined for flea infestation or given insecti-

dal treatment. Results for animals from multiple-animal households and single-animal households were evaluated separately.

### Statistical Analysis

The homogeneity of cases regarding species, sex, age, haircoat length, and body size was evaluated by the nonparametric chi-square ( $\chi^2$ ) or Fisher's exact test in which the expected value is  $<5$ . Comparisons of flea infestation and clinical signs in individual animals over time as well as between multiple- and single-animal households were done using the ordinal score assigned (0, 1, 2, or 3). The analysis was performed by the nonparametric, Friedman two-way ANOVA test. The presence of a significant probability over time was in turn compared by Wilcoxon's matched-pairs signed rank test with a correction of significance by Bonferroni's test. For the comparison between groups (multiple-animal households versus single-animal households) the  $\chi^2$  test or Fisher's exact test was used.

The dermal safety observed over time by the evaluation of discoloration, alopecia, erythema, and hyperkeratosis was described by frequency tables using the dichotomous answers yes (present) and no (absent).

General safety—observed by the possible presence of adverse events—was analyzed by descriptive tables. Whenever allowed for by the numbers, a comparison was performed by the  $\chi^2$  test.

The hypothesis null of the treatment was rejected based on a probability level of  $P < .05$ , two-tailed  $\alpha$ . All obtained results, both for statistical comparisons and synoptic tables, were computed by using the Statistical Package for the Social Sciences. All cases of incorrect protocol implementation were excluded from the statistical analysis.

## RESULTS

### Parasitologic Examinations

The most diffuse flea species identified on

the animals was *Ctenocephalides felis*, which accounted for 88.6% of the examined samples. The remaining specimens were *C. canis* (10%), *Pulex irritans* (1.3%), and *Nosopsylla* spp. (0.1%). Ninety-five percent of cats and 88.5% of dogs were infested solely by the species *C. felis*; single-species infestations from *C. canis* were observed in 9% of dogs and 4.1% of cats. Most infestations (95% of cats and 90.5% of dogs) were caused by a single species.

### Estimate of Fleas

At the start of the study (day 0), before treatment, animals from single-animal households were classified as follows: 37.9% of dogs and 44.9% of cats had mild infestations, 42.6% of dogs and 43.8% of cats had moderate infestations, and 19.5% of dogs and 11.3% of cats had heavy infestations. In comparison, 24.3% of dogs living in multiple-animal households had heavy infestations (>20 fleas). Contrary to what emerged for dogs, cats from single- and multiple-animal households had no statistically significant differences in degree of flea infestation on day 0. On day 1 after treatment, 60.4% of dogs (Table 1) and 57.2% of cats (Table 2) from single-animal households were completely free of fleas. In the other animals of this group, the flea infestation was markedly reduced, leaving 31% of dogs and 35.3% of cats with a mild infestation and 7.3% of dogs and 6.5% of cats with a moderate infestation. A heavy infestation was found in only 1.3% of dogs and 1% of cats. At the examinations on days 14, 21, and 28 after treatment, 95.2%, 98.3%, and 93.2% of dogs and 95.6%, 97.6%, and 93.2% of cats were free of fleas, whereas percentage values for moderate or heavy flea burdens ranged from 0.17% to 0.5% in dogs and reached a maximum of 0.7% in cats. The percentage change of mean values was >95% on days 14, 21, and 28 for flea counts in both dogs and cats, while the de-

creases were 72.8% in dogs and 69.1% in cats on day 1 (Tables 1 through 4).

In animals from multiple-animal households, the percentage of dogs free of fleas increased significantly on days 14 and 21 after treatment. On day 28, the percentage tended to decrease but the number of animals free of fleas remained >82.9% of the dog sample and >84.6% of the cat sample. For cats the average percentage decrease of mean values indicated a percentage reduction versus day 0 higher than 90% at days 14, 21, and 28. The comparison between the mean values calculated for both groups of dogs and cats revealed a statistically significant difference in favor of the animals from single-animal households at all examinations on days 14, 21, and 28 (Tables 1 and 2).

### Clinical Signs

In animals from single-animal households, clinical signs on day 0 included pruritus (85.2% of dogs and 75.7% of cats), which was rare in 34.4% of dogs and 39.7% of cats; frequent in 43.2% of dogs and 30.5% of cats; and continual in 7.6% of dogs and 5.5% of cats. From day 1 the signs decreased progressively to a significant extent in both species. At the end of the study (day 28), 81.1% of dogs and 83.5% of cats did not display itching; 17.1% of dogs and 16.5% of cats manifested it occasionally. Only 1.8% of dogs displayed frequent itching, and none of the dogs displayed continual itching; in cats these categories of itching disappeared, starting at day 14. The percentage of change, calculated from the score means, indicated a decrease higher than 85% for both species at the end of the study.

In animals from multiple-animal households on day 0 of the study, pruritus was present in 79.7% of dogs and 73.0% of cats. Itching was rare in 31.4% of dogs and 36.2% of cats, frequent in 38.5% of dogs and 32.2% of cats, and continual in 9.8% of dogs and 4.6% of cats.

**TABLE 1. Dogs without Fleas by Study Day\***

<i>Days</i>	<i>0</i>	<i>1</i>	<i>14</i>	<i>21</i>	<i>28</i>
Single-animal households (No. of dogs)	0% (604)	60% (365)	95% (574)	98% (593)	93% (561)
Multiple-animal households (No. of dogs)	0% (1335)	51% (678)	88% (1173)	92% (1228)	83% (1105)

\*The differences were significant ( $P < .001$ ) between the two groups on days 1, 14, 21, and 28.

**TABLE 2. Cats without Fleas by Study Day\***

<i>Days</i>	<i>0</i>	<i>1</i>	<i>14</i>	<i>21</i>	<i>28</i>
Single-animal households (No. of cats)	0% (291)	57% (167)	96% (279)	98% (285)	93% (272)
Multiple-animal households (No. of cats)	0% (1042)	54% (563)	89% (931)	91% (952)	85% (883)

\*The differences were significant ( $P < .01$ ) between the two groups on days 14, 21, and 28.

**TABLE 3. Mean Efficacy\* of Flea Control on Dogs**

<i>Days</i>	<i>0</i>	<i>1</i>	<i>14</i>	<i>21</i>	<i>28</i>
Single-animal households (604 dogs)	0%	73%	97%	99%	96%
Multiple-animal households (1335 dogs)	0%	65%	93%	96%	90%

\*The mean efficacy was defined as the percentage variation of the average scores.

**TABLE 4. Mean Efficacy\* in Flea Control on Cats**

<i>Days</i>	<i>0</i>	<i>1</i>	<i>14</i>	<i>21</i>	<i>28</i>
Single-animal households (291 cats)	0%	69%	97%	99%	95%
Multiple-animal households (1042 cats)	0%	64%	93%	95%	90%

\*The mean efficacy was defined as the percentage variation of the average scores.

Itching tended to decrease progressively in both species to a significant extent beginning on day 1 after treatment. At the end of the study (day 28), 78.7% of dogs and 81.2% of cats did not display itching, 18% of dogs and 17.5% of cats showed it occasionally, 3.1% of dogs and 1.3% of cats showed it frequently, and 0.2% of dogs and none of the cats displayed it continually. The difference between the two dog groups was significant on days 0 and 1 but lacked significance at the other examination times. In the two cat groups the difference was not significant any time.

Alopecia also improved progressively in dogs and cats during the 4-week trial. In fact, at the beginning of the study the sign was present in 28.5% of dogs and 21.9% of cats from single-animal households, among which 3.3% of dogs and 2.4% of cats had severe alopecia. On day 28, alopecia persisted in almost 7% of the animals, with only one severe case in each species. The mean of the scores assigned to each class of severity showed a statistically significant decrease from day 1 in both dogs and cats from single-animal households. The percentage change for alopecia, calculated from the means, revealed a decrease of 81.8% for dogs and 73.9% for cats on day 28 in this group.

In comparison, 27.7% of dogs from multiple-animal households had alopecia. Of those, 2.9% were severe cases. In cats from multiple-animal households, 21.2% showed signs of alopecia; 2.3% of these animals had severe symptoms. On day 28, alopecia was no longer present in 90% of these dogs and 94% of these cats but it persisted mildly or moderately in other subjects. None of the dogs and one of the cats still had se-

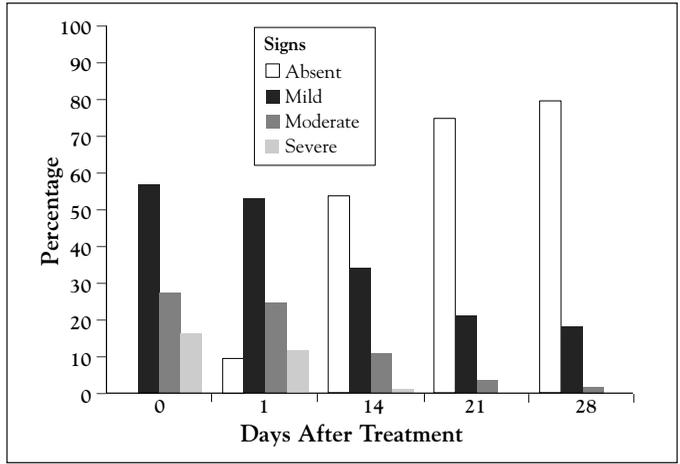


Figure 1. Flea allergy dermatitis in 688 dogs from multiple-animal households.

vere alopecia. The comparison of mean values of alopecia between dogs from single-animal households and multiple-animal households revealed statistically significant differences only on day 28. However, the two cat groups lacked statistical differences at the relevant times.

FAD was observed in 38.4% of dogs and 26.1% of cats from single-animal households before treatment. At the end of the observation period, only 5.8% of dogs and 4.8% of cats were suffering from FAD, with a reduction in the overall number of affected animals of 85% in dogs and 81.5% in cats. The trend of decrease in mean values was statistically significant for both species in this as well as in the other clinical signs, right from day 1. The percentage change indicated a decrease of the symptoms of FAD >88% in dogs and >83% in cats at the end of the study.

In animals from multiple-animal households, FAD was observed in 34.3% of dogs and 23.8% of cats before treatment. At the end of the trial, only 7.8% of these dogs and 5.1% of these cats showed signs of FAD, while the number of animals without FAD had increased from 65.7% to 92.2% in dogs and 76.2% to 94.9% in cats (Figures 1 and 2).

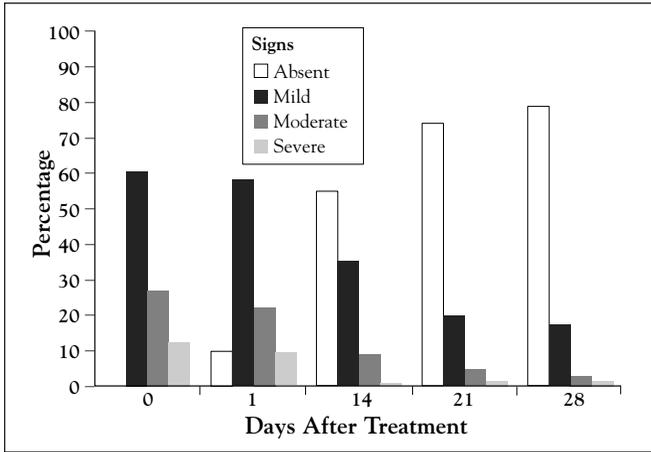


Figure 2. Flea allergy dermatitis in 323 cats from multiple-animal households.

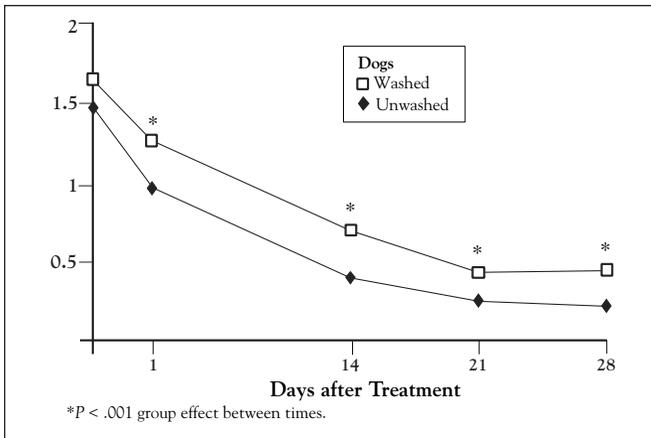


Figure 3. Itching: comparison between washed and unwashed dogs.

### Washed and Unwashed Dogs

Although the owners were requested not to wash the animals throughout the study, 224 dogs underwent washing or shampooing after treatment. In dogs a comparison of decreases in flea counts at the different study times indicated an absence of statistically significant differences between dogs that underwent at least one washing after treatment (11.5%) and dogs that did not. In some cases, dogs were washed

repeatedly (2 to 4 times) during the study period. Subjects that were washed showed a more gradual and less significant relief of itching, alopecia, and FAD than unwashed subjects (Figures 3 through 5). FAD was more frequent in the group of dogs whose owners later washed them than was the case in dogs that were unwashed. This difference remained highly significant throughout the observation period (Table 5).

### Haircoat Length and Body Size

The findings in this study indicate that haircoat length (short, medium, long) and body size (small, medium, large) do not interfere with the efficacy of treatment with imidacloprid. No statistically significant differences occurred in these different groups.

### Drug Interactions/Side Effects

No signs of reaction were found at the application site in treated animals throughout the study. Furthermore, there were no signs of adverse reactions

when imidacloprid was used in conjunction with other nonparasite drugs.

### DISCUSSION

The objective of the study described here was to assess the efficacy of a topical solution of imidacloprid for the treatment of natural flea infestations in dogs and cats under field conditions. To date, various flea control compounds have been used to control adult fleas on pets.

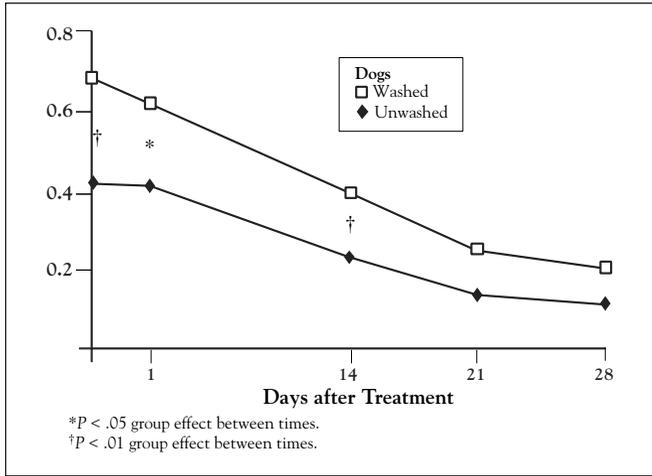


Figure 4. Alopecia: comparison between washed and unwashed dogs.

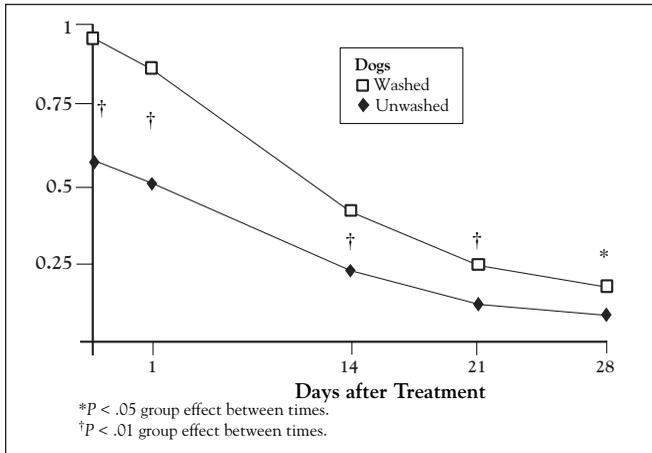


Figure 5. Flea allergy dermatitis: comparison between washed and unwashed dogs.

However, many flea populations have developed high levels of resistance to several insecticides.<sup>17</sup> New substances, such as insect growth regulators, have little or no adulticidal effect and may require extended periods to achieve acceptable levels of flea control.<sup>8-10</sup> It should be pointed out that the biology of *C. felis* is very complex, with only a small proportion of the

population residing on the animal host at any given time. The cycle of *C. felis* lasts an average of 14 to 17 days under adequate conditions of temperature and humidity, such as those in most owners' homes.<sup>2</sup> Therefore long-term control is often difficult to achieve.

During this study, the efficacy of imidacloprid was evaluated for 28 days after treatment. The trial indicates that a 10% topical solution has strong adulticidal action, killing fleas to a significant extent within the first 24 hours of application. In addition, although imidacloprid exerts no repellent action, it showed a high residual efficacy, which protects dogs and cats from single-animal households from reinfestation for at least 4 weeks to more than 95%. It is evident that treatment with imidacloprid interrupts the reproductive cycle of fleas by preventing the coupling of adults, laying of new eggs, and development of young adults and other roaming forms present in the environment.

It has been shown that fleas observed on animals 24 hours after treatment are the consequence of reinfestation phenomena rather than residual fleas.<sup>11-13,16</sup> This finding is confirmed by the increasing percentage of animals free from fleas or with moderate infestations on days 14 and 21 in this study. On day 28, the percentage tended to decrease, although the number of animals free from fleas remained at a high level, thus indicating good long-term activity of imidacloprid. This also applies when

**TABLE 5. Mean Efficacy\* in Controlling Flea Allergy Dermatitis in Washed and Unwashed Dogs**

<i>Days</i>	<i>1</i>	<i>14</i>	<i>21</i>	<i>28</i>
Washed (224 dogs)	67%	94%	97%	92%
Unwashed (1715 dogs)	66%	92%	96%	89%

\*The mean efficacy was defined as the percentage variation of the average scores.

the product is used on animals living in environments where the parasite cycle remains constantly active, as indicated by the results for animals from multiple-animal households.

Unlike experimental studies in which animals are infested and then treated while in an uninfested environment, after treatment this study reintroduced animals into the same environment from which infestation arose. Even under such conditions the mean infestation severity 24 hours after treatment shows a high decrease in both dogs and cats.<sup>18</sup> Only a small percentage of animals from both single- and multiple-animal households with severe flea infestations before administration of imidacloprid were still infested by >20 fleas after 24 hours. As expected, the comparison between the mean values calculated at all checks revealed a statistically significant difference in both dogs and cats in favor of animals from single-animal households, indicating a greater reduction in the presence of fleas. The efficacy of treatment with imidacloprid was also confirmed by the quick relief of clinical signs and the complete remission of itching and alopecia on day 28 after treatment in most of the dogs and cats, whether or not the animals were from single- or multiple-animal households.

Another particularly important aspect is represented by results obtained from subjects that presented with symptoms of FAD at the be-

ginning of the study. Control of the etiologic agent both on the host and in the environment also induced a complete remission of FAD in a significant number of animals during the 28 days after product application. Furthermore, the study revealed that such factors as body size of the animal and haircoat length in both dogs and cats as well as washing of dogs do not modify the impact of treatment. Clinical observations indicated that imidacloprid is well-tolerated by both dogs and cats; no side effects or interactions between imidacloprid and vaccinations or drugs were reported.

## ■ CONCLUSION

Findings obtained during this study confirm that treatment with a 10% topical solution of imidacloprid (Advantage®) is safe and well-tolerated in both dogs and cats. Efficacy of the product was expressed in an immediate and residual adulticidal action strong enough to eliminate any fleas hatched within 24 to 36 hours after application and then to prevent their reproduction. The product also exerted effective control of fleas for at least 4 weeks regardless of sex, size, haircoat length, and living conditions of treated animals and with no need to use additional environmental treatments. Accordingly, treatment with Advantage® was also shown to significantly reduce flea infestation-inflicted dermatologic lesions.

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