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SHORT COMMUNICATION

Assay of two 10% (w/v) fipronil spot-on formulations against feline infestations with *Ctenocephalides felis*

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A new fipronil-based spot-on formulation was evaluated against experimental flea infestations in cats in two studies. In both studies, eight cats served as negative controls (groups 1 and 4); on day 0, eight cats were treated with a 10% w/v fipronil-based spot-on solution (Effipro Spot-on, 0.5 ml per cat, groups 2 and 5) and eight cats served as positive controls (Frontline Spot-on, 0.5 ml per cat, groups 3 and 6). Each cat was infested on day – 1 with 50 fleas (study 1) and weekly (day 7–day 56) with 100 fleas (study 2). Geometric mean flea counts obtained 48 h after the treatment or each re-infestation were reduced by 99.0 and 98.3% in groups 2 and 3, respectively, on day 2, compared to the negative control group. Cats were protected from re-infestations with an efficacy >99% for 58 days in group 5 and for 37 days in group 6.

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Fleas remain the most common parasites in cats.^{1–4} In addition to the irritations due to their bites, including in some animals an allergic dermatitis⁵ (the so-called flea allergic dermatitis or flea allergy dermatitis (FAD)), fleas can also carry zoonotic diseases.⁶ Introduced in 1994, fipronil has been a leader on the flea market products for dogs and cats ever since. First available as a 0.25% w/v spray,⁷ fipronil became then marketed as a spot-on formulation⁸ and eventually was combined with S-methoprene, also in a spot-on.⁹ More recently, pyriprole from the same chemical group had been launched and is available as a spot-on.¹⁰ Finally, as fipronil's patent has recently expired in some countries, new fipronil-based products are now present on the market.¹¹

Two studies were conducted to evaluate the immediate (study 1) and sustained (study 2) efficacies and the tolerance of a new spot-on formulation (Effipro Spot-on; Virbac SA) with the same qualitative and quantitative composition in terms of active ingredient (fipronil) as the original product (Frontline Spot-on Cats; Merial) but with different vehicles. The efficacy was evaluated against experimental infestations with *Ctenocephalides felis* in cats. A positive reference control group included cats treated with the original product.

Materials and methods

Animals

According to the European Agency for the Evaluation of Medicinal Products' requirements (EMA/CVMP/005/00-FINAL-Rev1), at least six animals were included in each group and each animal was individually housed. They were fed a commercial cat diet and water was supplied ad libitum.

Study groups were coded to blind the staff performing post-treatment assessments and observations.

Study 1: Twenty-four (12 females and 12 males) domestic shorthair cats between 9 months and 5 years of age and weighing from 2.5 to 4.9 kg at day – 8 were initially included. The cats were ranked within gender in descending order of individual bodyweight. Within each gender, animals were then allocated to blocks of three cats each. Within each block, cats were allocated randomly into three groups of eight (groups 1, 2 and 3). They were acclimatised for 9 days prior to treatment.

Study 2: Twenty-four (18 females and 6 males) domestic shorthair cats over 4 months of age and weighing from 1.9 to 4.1 kg at day – 7 were initially included. The cats were ranked within gender in descending order of individual flea counts. Within each gender, animals were then allocated to blocks

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of three cats each. Within each block, cats were allocated randomly into three groups of eight (groups 4, 5 and 6). They were acclimatised for 7 days prior to treatment.

Experimental infestations

Two laboratory-bred strains of *C felis*, routinely fed on cats, were used for the infestations.

Study 1: Two infestations were scheduled: one preliminary infestation (40 fleas/cat) was performed in the pre-treatment period on day - 9 for validation, cats were re-infested on day - 1 with 50 fleas each.

Study 2: Cats were infested on days - 7 (preliminary infestation), 7, 14, 21, 28, 35, 42, 49 and 56 with about 100 fleas/cat and per infestation.

Treatments

Each study was a parallel-arm, randomised block design, single site and blinded controlled study. The animals were not treated by anyone involved in the post-treatment assessments and observations.

Study 1: The cats in groups 1 were not treated. The cats in groups 2 were treated with a 10% w/v fipronil-based spot-on solution (Effipro Spot-on; Virbac SA) at a dosage of 0.5 ml per cat. The cats in groups 3 were treated with the original fipronil spot-on (Frontline Spot-on Cat, Merial) at a similar dosage. Study 2: The cats in groups 4 were not treated. The cats in groups 5 were treated with a 10% w/v fipronil-based spot-on solution (Effipro Spot-on; Virbac SA) at a dosage of 0.5 ml per cat. The cats in groups 6 were treated with the original fipronil spot-on (Frontline Spot-on Cat; Merial) at a similar dosage.

The solution used in groups 2 and 5 had the same qualitative and quantitative composition in terms of active ingredient (fipronil) as Frontline Spot-on but some vehicles were different. Both products were applied topically as two spots of equal volumes distant to 2–3 cm on the skin between the shoulders. Care was taken to avoid wetting the hair and applying the dose to an area where the animal could lick it off. Concurrent treatments unlikely to interfere with the study were acceptable (antimicrobials, vitamins and mineral supplements and sedatives) and the treatment details were recorded. Substances that may have had an insecticidal or acaricidal activity (eg, medicated shampoos) were not allowed.

Assessments

Study 1: Each animal was submitted to a full clinical examination on days - 8, 0 (1 h and 6 h after dosing), 1 and 2. Additionally, cats were examined

on an approximately hour basis for 4 h after treatment for possible adverse reactions. The skin at the administration site was assessed for cosmetic changes for 48 h after treatment, alopecia, erythema and oedema. Any cosmetic changes (eg, clumping, matting, discolouration) were recorded.

Study 2: In study 2, full clinical examinations were performed on days - 7, 27 and 55.

Forty-eight hours after the treatments and 48 h after each challenge, the population of remaining fleas was assessed for each animal. Three operators were involved in the assessment of a specific animal. One person handled and restrained the cat, a second was responsible for combing the cat and a third person was responsible for quantifying the fleas recovered from each comb and recorded the data. During combing, a fine-toothed flea comb was used to recover fleas present in the cat's fur. The method of combing included several strokes of the comb in each area of the animal, each time moving in the same direction, following the pattern of the hair coat. Movement from one part of the cat's fur to the next was via strokes overlapping each other, so that no area of fur was missed. After completion of the combing procedure for all body areas, the whole procedure was repeated so that all areas were combed twice. Fleas which were collected were counted and were not replaced on the animals.

Statistics

The two studies were analysed separately. For all analyses, the significance threshold was set to $\alpha = 0.05$. In both studies, the three groups were described and compared before treatment (baseline) on the following criteria: bodyweight, sex and flea count. Qualitative parameters were analysed using a Fisher's exact test and quantitative parameters were analysed using a Kruskal-Wallis test. Arithmetic and geometric mean flea counts were calculated for each of the six groups at each time point. For groups 2, 3, 5 and 6, efficacy was calculated at each time point using the mean according to Abbott's formula: $\text{Efficacy (\%)} = 100 \times (\text{mean}_{\text{control}} - \text{mean}_{\text{treated}}) / \text{mean}_{\text{control}}$. The groups were compared using an analysis of variance (ANOVA) with a treatment effect after logarithmic transformation of flea (count + 1) data.

Results

In both studies, the three groups were homogenous at baseline on the following criteria: sex, bodyweight and flea count (Table 1). No adverse events were recorded in any of the treatment groups that could be related to the administration of either product. The arithmetic mean numbers of fleas that were present in the hair coat of the untreated control cats and on treated animals 48 h after each infestation are graphically illustrated in Fig 1. The efficacy, based on

Table 1. Mean (sd; $n = 8$), median, minimal and maximal values of weight and pre-treatment flea count from cats treated with one of the two 10% w/v fipronil-based spot-on solutions or left untreated.

Variable	Study	Treatment group	Mean (std)	Median	Min–max
Weight (kg)	1	Negative control	4.0 (0.7)	4.1	3.0–4.8
		Effipro	3.9 (0.8)	4.0	2.5–4.8
		Frontline	3.9 (0.7)	4.0	2.8–4.9
	2	Negative control	2.5 (0.2)	2.5	2.3–2.8
		Effipro	2.6 (0.7)	2.2	2.0–3.8
		Frontline	2.7 (0.8)	2.3	1.9–4.1
Pre-treatment flea count*	1	Negative control	27.5 (3.2)	27.5	23–30
		Effipro	28.5 (4.3)	29	21–34
		Frontline	28.6 (4.2)	28	23–35
	2	Negative control	59.8 (8.9)	58.5	46–74
		Effipro	61.4 (7.5)	60.0	52–71
		Frontline	61.4 (8.9)	58.5	53–79

*Pre-treatment infestations were performed with 40 fleas/cat in study 1 and 100 fleas/cat in study 2.

geometric means, of both formulations of fipronil is summarised in Table 2.

Study 1: All animals of group 2 (Effipro) and group 3 (Frontline) had clumping of the hairs at the application site 1 and 6 h after application. Greasiness of the hair was observed at the application site in six animals of group 2 and five animals of group 3, 1 and 6 h after the treatment. Five cats assigned to the Effipro group had white deposit on the hair on the application site 24 h after the application. That white deposit was still slightly present on three cats at 48 h following treatment.

Experimental infestations with *C felis* were successful, with a mean percentage recovery of *C felis* on the control cats of 70.5 on day 2. The application of the two formulations of fipronil led to the almost

complete eradication of all fleas when cats were examined on day 2: only six fleas collected from two cats in group 2 and nine fleas collected from three cats in group 3 were recovered. The difference between the two groups was not statistically significant ($P = 0.609$).

Study 2: One cat from the control group developed severe signs consistent with FAD; it was excluded on day 17 and not replaced.

Experimental infestations with *C felis* were successful, with a mean percentage recovery of *C felis* on the control cats ranging between 53 (day 16) and 70.3 (day 23) percent 48 h after each infestation. Cats in group 5 were protected from re-infestations for 58 days with an efficacy of at least 99%. Cats in group 6 were protected from re-infestations for 44 days with an efficacy

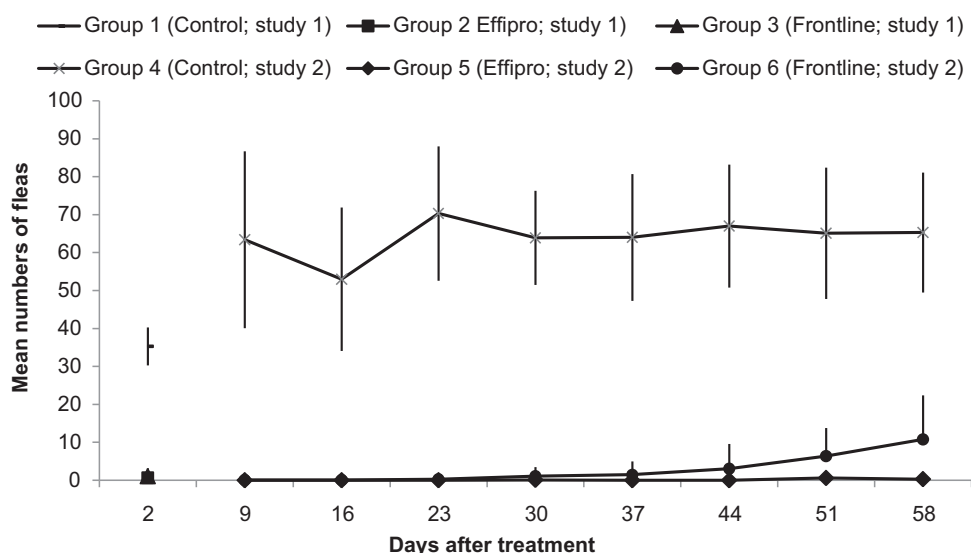


Fig 1. Arithmetic mean standard deviation (sd) *Ctenocephalides felis* counts 48 h after treatment with two 10% w/v fipronil-based spot-on solutions on day 0 (study 1) and 48 h after weekly re-infestation with 100 unfed adult fleas over 8 weeks (study 2). In study 1, infestations on day - 1 were performed with 50 fleas/cat.

Table 2. Mean geometric efficacy (%) of two 10% w/v fipronil-based spot-on solutions applied to cats experimentally infested with *Ctenocephalides felis*, calculated 48 h after the treatment (study 1) and 48 h after each weekly re-infestation over 8 weeks (study 2).

Formulation	Days after treatment								
	2	9	16	23	30	37	44	51	58
Effipro	99.0	100	100	100	99.9	100	100	99.3	99.7
Frontline	98.3	99.8	99.8	99.7	99.1	99.0	98.2	93.7	90.7

of at least 98.2%, which was reduced to 93.7% on day 51 and 90.7% on day 58. Differences between the two groups were significant on days 44, 51 and 58 ($P = 0.024, 0.0016$ and 0.0001 , respectively).

Discussion

Both products were well tolerated by all the animals who received the treatments. Only cosmetic changes were seen at the application site (greasiness and clumping of the hair coat for both formulations, white deposit for Effipro Spot-on); they resolved by 24–48 h.

Effipro Spot-on and Frontline Spot-on were both very effective to treat flea infestation in cats (efficacies of 99.0 and 98.3%, respectively, on day 2). This level of control is comparable to the efficacy of Frontline Spot-on reported in various similar studies against experimental flea infestations in cats^{11–14} or in semi-field studies.^{15,16} Comparable results were obtained with another fipronil-based spot-on against experimental infestations in a group of six cats with an efficacy >99% for 21 days.¹¹ Finally, these results are in agreement with those previously obtained in two studies conducted in a similar manner on dogs experimentally infested with fleas¹⁷ and ticks,¹⁸ respectively.

Under the conditions of study 2, both treatments provided long-lasting residual protection against flea infestations (58 and 44 days for Effipro Spot-on and Frontline Spot-on, respectively). However, the standardised procedures, the absence of continuous re-infestations from the environment or from other animals, the climatic stability, the absence of skin interventions/lesions, which could impair the diffusion of the product and/or its persistence on the skin, make ideal the conditions of the present trial. Therefore, under field conditions, such a long-lasting residual protection is unlikely. Recommendations of monthly applications are commonly made, based on previous field studies.^{15,19,20}

Both Effipro Spot-on and Frontline Spot-on are 10% w/v fipronil-based spot-on solutions but some of their vehicles are different. The present study shows that despite different vehicles, the two formulations were equally able to eradicate flea infestation, to prevent new infestations and that they were equally well tolerated.

Conflict of interest

MC Cadiergues is consultant for Virbac SA.

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