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Efficacy and safety of sarolaner (Simparica™) against fleas on dogs presented as veterinary patients in the United States

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ABSTRACT

The efficacy and safety of a novel isoxazoline parasiticide, sarolaner (Simparica™), for the control of fleas on dogs was evaluated in a randomized, controlled clinical study conducted in 19 general veterinary practices throughout the United States. Four hundred and seventy nine (479) dogs from 293 households were enrolled. Each household was randomly assigned to treatment with either sarolaner oral tablets (Simparica™, Zoetis) at the proposed label dose or an approved comparator product at the label dose (spinosad, Comfortis®, Elanco). Dogs were dosed by their owners at home on Day 0 and on approximately Days 30 and 60. Dogs were examined at the clinics for general health, flea and tick infestation, and clinical signs of flea allergy dermatitis (FAD) at the initial visit and Days 14, 30, 60 and 90. Blood was collected for clinical pathology at screening and Day 90.

Sarolaner was well-accepted by dogs with the majority of flavored chewable tablets (91.5%) accepted free choice, by hand or in food. Geometric mean live flea counts were reduced by >99% at the first time measured (14 days) after initiation of treatment and continued to reduce through the study. Treatment success (proportion of dogs with ≥90% reduction in fleas) for the sarolaner-treated dogs was superior to that for spinosad-treated dogs at Days 14 and 30 and non-inferior on Days 60 and 90 ($P \leq 0.025$) The rapid reduction in flea infestations resulted in a similar rapid resolution of the clinical signs associated with FAD. Sarolaner chewable tablets were well tolerated with no treatment related adverse reactions. Most of the clinical signs reported were consistent with allergies and dermatitis or sporadic occurrences of conditions commonly observed in the general dog population. A wide variety of concomitant medications, including many commercially available heartworm preventatives and other anthelmintic drugs, were administered to study dogs and all were well tolerated.

Sarolaner administered orally to provide a minimum dosage of 2.0 mg/kg (range 2–4 mg/kg) once monthly for three consecutive treatments was safe and effective in the treatment and prevention of natural infestations of fleas and resulted in a substantial improvement of clinical signs associated with FAD.

1. Introduction

The cat flea, *Ctenocephalides felis felis* is one of the most important ectoparasites of dogs and cats worldwide (Rust and Dryden, 1997). Prevention and control of fleas is a cornerstone of preventive veterinary medicine and effective flea control relies on fast onset of action, consistent coverage over the dosing interval, and pet owner compliance. Adult fleas are blood feeders and create local irritation caused by feeding and heavy infestations can lead to anemia. Fleas are intermediate hosts for the dog tapeworm and transmit a number of diseases including zoonoses, and in the absence of primary hosts will readily feed on humans (Dryden, 1989; Krämer and Menke, 2001). In general, the clinical signs associated with flea bites (flea bite dermatitis), including pruritus, papules, erythema, scaling, alopecia and dermatitis/pyodermatitis, are transient. However, in some dogs, exposure to fleas may lead to a more serious condition of flea allergy dermatitis (FAD) which is the most common dermatologic disease of domestic dogs (Dryden, 2009). In the FAD dog, once sensitization has occurred, recurrence of signs can be initiated by just a small number of bites, although the threshold of sensitivity varies between individual dogs (Carlotti and Jacobs, 2000). Successful management of the FAD case ultimately depends on eliminating fleas as they are the source of allergenic challenge, and year-round prevention of flea infestations is recommended (Olivry et al., 2010). Although commercial products for the prevention of flea infestations are available to veterinarians and pet owners, there remains

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opportunity to provide new options which could improve speed of kill, consistency of coverage and client compliance.

Sarolaner is a novel parasiticide belonging to the isoxazoline class. Laboratory studies have confirmed that a minimum sarolaner dose of 2 mg/kg begins killing fleas three hours after treatment and is highly effective for the treatment and control of existing cat flea infestations and the persistent control of fleas on dogs for 35 days after treatment (Six et al., 2016a,b). Here, we report on a clinical field study conducted to evaluate the efficacy and safety of sarolaner (Simparica™, Zoetis) flavored, chewable tablets administered orally for three months at a minimum dosage of 2.0 mg/kg (range–4 mg/kg) compared to spinosad oral tablets (Comfortis®, Elanco) administered per label for the treatment and prevention of natural flea infestations in client-owned dogs.

2. Materials and methods

The study was conducted in accordance with the World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestation on dogs and cats (Marchiondo et al., 2013) and complied with Good Clinical Practices (EMEA, 2000). The protocol was reviewed and approved by the Zoetis Institutional Animal Care and Use Committee.

2.1. Animals

The patient population was recruited from veterinary practices located in various geographical regions of the United States, representing the range of typical clients for North America. Patients came from diverse households and living conditions, thus dogs lived indoors only, outdoors only, or both indoors and outdoors. Dogs came from single dog households and households with other dogs (up to a total of three dogs) and/or cats. There were no breed or gender restrictions, but dogs intended for breeding or that were pregnant or lactating were not eligible for enrollment. For inclusion in the study at least one dog in the household had to harbor at least 10 fleas. Dogs had to be at least 8 weeks of age and weigh at least 1.25 kg. Dogs less than 14 weeks of age and allocated to the spinosad treatment group were excluded from enrollment in order to comply with the Comfortis® label requirements. Dogs with pre-existing conditions under stable veterinary management could be included as could dogs with clinical signs of flea infestation. Dogs with existing uncontrolled medical conditions that might confound the study were excluded. Dogs could not have been treated with any products with residual activity against fleas within 30 days or any short-acting ectoparasiticide within 7 days of the start of the study.

2.2. Experimental design and methods

The study was a single-masked, positively-controlled clinical trial with a randomized complete block design. For a household to be included, at least one dog had to have 10 or more live fleas. Where more than one dog met this criterion, a primary dog was randomly selected, and the other dogs were designated as supplementary dogs. All dogs in a household received the same treatment as the primary dog and were included in safety evaluations. Only primary dogs were included in the efficacy evaluations. Households were allocated randomly to treatment with sarolaner or spinosad in a ratio of 2:1 based on the order of enrollment. Dogs were housed and maintained under their normal home conditions for the duration of the study. Other than the experimental treatments, no products (systemic, premise, and/or over-the-counter treatments including insecticidal shampoos or collars) that had activity against fleas were permitted to be used on any animal in the household for the duration of the study. Non-insecticidal shampoos were permitted to be used; however primary dogs could not be bathed within three days of an assessment. The use of corticosteroids was permitted, but dogs that received corticosteroids during the study were excluded from the skin assessment analysis.

Eligibility for inclusion in the study was determined at the initial screening visit. Dogs were weighed, given a physical exam, had blood collected for hematology and blood chemistry testing, and had urine collected for urinalysis to assess general health. Flea counts were conducted by personnel trained to a standardized methodology. The dogs were thoroughly flea-combed using a commercial fine tooth flea comb to remove and count fleas. Dogs were systematically combed while standing starting from the head, then proceeding caudally along the dorsum. The dog was then placed on each side and then on its back for combing of the sides and ventral surfaces. Dogs were repeatedly combed until no fleas were recovered within a 5 min period. Each dog was examined for a minimum of 10 min. Fleas maintaining an upright orientation/or moving in a coordinated manner were considered to be live. Only live flea counts were recorded. Any ticks, live or dead, removed during the flea-combing process, were placed into two appropriately marked containers. After combing was completed, the dog's body was examined, using the thumb and forefingers, for any remaining ticks which were removed and placed in the appropriately marked containers. Ticks showing movement and responding to external stimuli were considered to be live. The ticks collected were submitted to a parasitologist for identification of species, sex, stage, and engorgement status. All personnel conducting observations or animal care, or performing the flea and tick counts were masked to treatment allocation.

All dogs in multi-dog households underwent these screening exams. The primary dog was identified and evaluated by the veterinarian for the presence and severity of the following clinical signs: pruritus, papules, erythema, scaling, alopecia, and dermatitis/pyodermatitis. Flea allergy dermatitis was diagnosed on the basis of the dog's history, the presence of these clincial signs, and the improvement in these signs at the completion of flea treatment (Daigle, 2005; Griffin, 2010; Ihrke, 2008).

If at the initial visit, a tick control product was requested or recommended, a placebo collar was dispensed for sarolaner-treated dogs or an amitraz containing collar (Preventic®, Virbac) was dispensed to dogs to be treated with spinosad. On subsequent visits, if tick control was requested or recommended, amitraz collars were dispensed to dogs in either treatment group. For households with cats, the use of a commercially available flea treatment in those animals was encouraged.

Eligible households were randomly allocated to treatment with either sarolaner or spinosad oral tablets on order of presentation to the clinic. Sarolaner tablets were provided in six different strengths to provide a minimum dosage of 2.0 mg/kg (range 2–4 mg/kg). Spinosad tablets were dispensed per label directions to provide a dose $\geq$30 mg spinosad/kg. Owners were provided with sarolaner and spinosad at the clinic, and then administered treatments and evaluated product consumption at home for all dogs in the household. Day 0 was defined as the day on which the primary dog received its first dose. All animals enrolled within the household were treated on the same day, and within one day of the clinic visit. The dose was offered or given at any time of the day. There were no restrictions regarding the prandial state at the time of sarolaner administration, therefore tablets could be administered with or without food. Spinosad was administered with the main meal of the dog in order to comply with the approved dosing directions for that product. In order to assess tablet palatability, owners were instructed to first offer the tablet(s) without food. If the tablet(s) were not consumed directly, then they were to be offered in a small amount of food. If the tablet(s) were not consumed with food, then