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Evaluation of the effectiveness of a novel oral formulation of sarolaner (Simparica™) for the treatment and control of fleas on dogs

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ABSTRACT

The efficacy of a single oral dose of a novel isoxazoline, sarolaner (Simparica™, Zoetis), for the treatment and control of flea infestations on dogs was confirmed in five laboratory studies. The studies were conducted using adult purpose-bred Beagles and/or mixed breed dogs. All animals were individually identified and housed, and were allocated randomly to treatment with either placebo or sarolaner (eight to 10 per group) based on pretreatment parasite counts. Three studies used cat flea (*Ctenocephalides felis felis*) strains recently isolated from the field from the US, EU, or Australia; in the fourth study a laboratory strain (KS1) with documented tolerance to a number of insecticides such as fipronil, imidacloprid, and permethrin was used. In the fifth study, dogs were infested with dog fleas, *Ctenocephalides canis*. Dogs were treated orally on Day 0 with a placebo or a sarolaner tablet providing a minimum dose of 2 mg/kg. Dogs were infested with approximately 100 unfed, adult fleas prior to treatment and at weekly intervals post-treatment. Comb counts were conducted to determine the numbers of viable fleas at 24 h after treatment and after each subsequent infestation. Efficacy against *C. felis* and *C. canis* was 99.8–100% from treatment through Day 35. In all five studies, elimination of existing infestations was achieved within 24 h after dosing, with only a single live *C. felis* found on one dog on Day 1. Similarly, control of flea challenges was achieved within 24 h after infestation throughout the 35 day study periods, with only single live *C. felis* found on two dogs on Day 28 in one study, and on a single dog on Day 35 in another study. There were no adverse reactions to treatment with sarolaner. These studies confirmed that a single oral dose of sarolaner at 2 mg/kg provided highly effective treatment of existing *C. felis* infestations and persistent control of *C. felis* on dogs for 35 days after treatment. Efficacy equivalent to that seen with *C. felis* was confirmed against *C. canis* and a known insecticide-tolerant strain of *C. felis*.

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1. Introduction

Flea infestations have been recognized for decades as a common burden for companion animals and their owners worldwide. *Ctenocephalides felis felis* (cat flea) is considered to be the most common ectoparasite of companion animals and has a worldwide distribution (Rust and Dryden, 1997). *Ctenocephalides canis* (dog flea) has a similar distribution, host spectrum, and biology to *C. felis* (Krämer and Menke, 2001) but is generally less commonly encountered. They are recognized as a major cause of pruritus in companion animals, are intermediate hosts for the dog tapeworm, *Dipylidium caninum,* and can transmit a number of pathogens including *Bartonella henselae* (Kwochka, 1987; Foil et al., 1998; Breitschwerdt and Kordick, 2000; Krämer and Menke, 2001; Breitschwerdt et al, 2010), *Bartonella clarridgeae* and *Bartonella koehlerae* (Chomel and Kasten, 2010), and *Rickettsia felis* (Horta et al., 2014). Adult fleas are blood feeders, penetrating the skin with their sucking mouthparts and injecting salivary antigens as they feed, and when present in

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large numbers are capable of causing anemia (Dryden, 1989). Given the high prevalence and the pathogenic and zoonotic potential of fleas (Beugnet and Franc, 2012), flea control should be a high priority in wellness programs targeted at maintaining the health of dogs and cats over their lifetime. Key objectives for flea-control programs include rapid speed of kill for existing infestations on the animal, prevention of re-infestation of the pet with on-going exposure, and rapid elimination of adult fleas prior to egg production (Carlotti and Jacobs, 2000). Successful control and prevention enhances the human-companion animal bond by preventing these irritating and debilitating parasites, controlling signs of flea allergy dermatitis in allergic animals, and helping protect pets and their owners from exposure to vector-borne pathogens by minimizing vector exposure.

Control of fleas depends upon chemical parasiticides and on-animal treatments generally applied as monthly spot-on applications have been the standard accepted method (Dryden and Payne, 2004; Rust, 2005). Spot-on treatments include active ingredients from a number of chemical classes, including phenyl pyrazoles, fipronil; neonicotinoids, imidacloprid; the pyrethroids, permethrin and phenothrin; and selamectin, an avermectin (Rust, 2005). There are also products such as the insect growth regulators, lufenuron, pyriproxyfen, and methoprene, that control fleas by disrupting the development of eggs and larvae. Fleas have developed resistance to a number of insecticides; pest management strategies to reduce further development of resistance have been proposed (Bossard et al., 1998; Ross et al., 1998; Rust, 2005) to actively manage the use of these products to attempt to preserve the effectiveness of these older active ingredients. Newer classes of oral formulations have been introduced and have gained acceptance for their convenience and consistent efficacy as these are unaffected by environmental factors (sun, bathing, swimming, *etc.*) and owner application variation that can impact efficacy of topical products. These oral products include spinosad (for fleas only) and the recently introduced isoxazoline compounds that provide control of both fleas and ticks (Robertson-Plouch et al., 2008; Rohdich et al., 2014; Shoop et al., 2014).

Sarolaner is an isoxazoline ectoparasiticide with insecticide/acaricide activity that has excellent efficacy against fleas on dogs following oral administration at a minimum dose of 2 mg/kg (McTier et al., 2016). Here we report a series of laboratory studies conducted to confirm the efficacy of sarolaner (Simparica™, Zoetis) given as a single oral dose to dogs for the treatment of existing flea infestations, and the persistent control of fleas for one month. These studies assessed efficacy *versus C. felis* strains representative of current field populations from the US, Europe, and Australia, and a European strain of *C. canis*. Further, efficacy of sarolaner was evaluated against a known insecticide resistant strain of *C. felis*, KS1, (Dryden, 1998; Payne et al., 2001; Bossard et al., 2002; Rust et al., 2002; Dryden et al., 2005, 2008).

2. Materials and methods

Five studies were conducted to confirm the efficacy of the proposed minimum label dose of 2 mg sarolaner/kg against existing flea infestations and weekly challenges up to 35 days after a single oral dose. Four studies evaluated *C. felis*, and in the fifth study efficacy was confirmed against *C. canis* (Table 1).

The studies were 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 (VICH guideline GL9) (EMEA, 2000). Study protocols were reviewed and approved by the local and/or Zoetis Institutional Animal Care and Use Committee.

2.1. Animals

The studies used purpose bred Beagle and/or mixed breed dogs of both sexes, ranging in age from 9 to 96 months and weighing from 6.0 to 26.0 kg (Table 1). All dogs had demonstrated good flea retention prior to treatment, were in good health at enrolment, and had not been treated with an ectoparasiticide for at least 60 days. Dogs were individually identified and housed in enclosures that conformed to accepted animal welfare guidelines and ensured no direct contact between dogs. Dogs were fed an appropriate maintenance ration of a commercial dry canine feed for the duration of the study. Water was available *ad libitum*.

2.2. Experimental design and methods

Dogs were acclimated to the study conditions for at least 14 days prior to treatment. The dogs were observed for general health at least once daily throughout the studies by personnel qualified through training and experience. A physical exam was performed on each dog by a veterinarian to determine health and suitability prior to inclusion in the study. For infestations, dogs were held and approximately 100 fleas were applied directly to the dogs and allowed to disperse into the hair coat. Flea counts were performed by personnel trained in the standard procedures in use at the test facilities. Protective gloves and clothing were changed between dogs and personnel conducting parasite or other observations were masked to treatment assignments. The dogs were thoroughly combed to remove fleas for counting. Fleas able to stand upright and/or move in a coordinated manner were considered live. Commercial fine-toothed flea combs were used. Dogs were systematically combed using repeated strokes while standing, starting from the head and proceeding caudally along the dorsum. The dog was then placed in lateral recumbency, followed by dorsal recumbency, for combing of the sides and ventral surfaces. Each animal was examined for a minimum of 10 min. Any animal on which fleas were found in the last five minutes was combed for an additional five minutes (one minute in Study 3).

Approximately one week prior to treatment, 20–22 dogs were infested with fleas. These dogs were then combed to count fleas 24 ± 2 h later. The 16 dogs (20 dogs in study 3) with the highest live flea counts were selected for inclusion in each study. The dogs were ranked by flea count and then randomly assigned to either placebo control or treatment with sarolaner.

Day 0 for each study was the day on which dogs were administered study treatment. On Day-1, all dogs were infested with fleas. On Day 0, the dogs were offered their normal ration of food ~20 min prior to dosing (one hour in Study 4). In Studies 1–5, dogs treated with sarolaner were administered a single or combination of tablets from strengths of 5, 10, 20 or 40 mg to achieve the appropriate dose (as close as possible to 2.0 mg sarolaner/kg without under dosing). Placebo-control dogs were dosed with similarly sized placebo tablets. In Study 4, 40 mg sarolaner tablets were individually shaved and/or sanded to deliver the minimum dosage of 2.0 mg/kg and control dogs received a single placebo tablet. To ensure complete dosing in these laboratory studies, all dogs were hand-pilled. Each dog was observed for several minutes to make sure the dose was swallowed and for any adverse events associated with administration, and then periodically for up to two hours for any signs of emesis. Dogs were observed for general health and any reaction to treatment approximately 1, 3, and 6 h after treatment on Day 0, then at least once daily for the remainder of the study.

On Day 1, approximately 24 h after treatment, each dog was examined and combed to count and remove fleas. Subsequently,

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