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Evaluation of the efficacy and safety of a novel formulation of metaflumizone plus amitraz in dogs naturally infested with fleas and ticks in Europe

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Abstract

The efficacy and safety of a novel spot-on formulation of metaflumizone plus amitraz (ProMeris®/ProMeris Duo® for Dogs, Fort Dodge Animal Health, Overland Park, KS) was assessed in dogs naturally infested with ticks and/or fleas in a multiregional, clinical field study. Nineteen veterinary clinics in Germany and 11 clinics in France enrolled patients to the study. One hundred eighty one dogs with tick infestation and 170 dogs with flea infestation (plus three dogs harboring both ticks and fleas) qualified as primary patients and were randomly allocated to one of two treatments in a ratio of approximately 2:1 for metaflumizone plus amitraz (minimum dosage of 20 plus 20 mg/kg) or fipronil (at the recommended label rate). Clinical examinations and baseline parasite counts were performed on Day 0 prior to treatment. Tick and/or flea counts and safety evaluations were repeated at intervals of about 2 weeks for 8 weeks. Both products resulted in consistent reductions in tick numbers (>81%) throughout the study, with metaflumizone plus amitraz giving consistently higher reductions in tick numbers. The efficacy against tick count compared with Day 0 was 97.6%, 93.5%, 89% and 94% at Day 14, 28, 42 and 56, respectively, for metaflumizone plus amitraz. The corresponding efficacies for fipronil were 86.3%, 81.1%, 84.8% and 86.1%. Within groups, the tick reduction was highly significant ($P < 0.0001$) compared to baseline at all observation periods. Both treatments resulted in consistent (>89%) and highly significant ($P < 0.0001$) reductions in flea numbers relative to the baseline counts throughout the study, although fipronil resulted in numerically higher reductions on each count day. The efficacy against fleas compared to baseline was 91.8%, 88.7%, 91.5% and 92.0% at Day 14, 28, 42 and 56, respectively, for metaflumizone plus amitraz. The corresponding efficacies for fipronil were 98.2%, 96.3%, 95.9% and 96.7%. Metaflumizone plus amitraz was highly effective in controlling existing infestations of fleas and ticks on dogs and was effective against reinfestation for at least 56 days. Metaflumizone plus amitraz showed a good tolerance profile in dogs.

Keywords: ProMeris®; ProMeris Duo®; Metaflumizone; Amitraz; Flea; Tick; Dog; Clinical field study

1. Introduction

Tick and flea infestations are the major ectoparasites affecting dogs. The main flea species found on dogs is *Ctenocephalides felis felis* (Rust and Dryden, 1997; Beck et al., 2006) and the major tick species affecting

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dogs in Europe include *Ixodes ricinis* and *Rhipicephalus sanguineus* (Ogden et al., 2000; Földvári and Farkas, 2005). In Europe, ticks tend to occur on dogs from early spring to late autumn and are important vectors for several diseases affecting dogs (e.g. borreliosis, ehrlichiosis, tick encephalitis and babesiosis) and humans (e.g. tick encephalitis, borreliosis). Fleas tend to occur on dogs from spring to winter in Europe and are known to be vectors for other diseases. Therefore, treatment against fleas and ticks is important to prevent both canine and human disease.

Metaflumizone is a new insecticide in the semicarbazone class of chemistry with potent activity against fleas (Takagi et al., 2007, this volume; Rugg and Hair, 2007, this volume) and no known cross-resistance to other chemistries (Salgado and Hayashi, 2007, this volume). Amitraz is a well-known formamidine acaricide (Hollingworth, 1976; Folz et al., 1986; Estrada-Pena and Ascher, 1999). A novel spot-on formulation containing metaflumizone plus amitraz (ProMeris®/ProMeris® Duo, Fort Dodge Animal Health, Overland Park, KS) applied as a single application to dogs to provide a minimum dose of 20 mg metaflumizone and 20 mg amitraz/kg provides at least 4 weeks control of fleas and ticks in laboratory studies (Rugg et al., 2007, this volume). The objective of this study was to evaluate the efficacy and persistency of the metaflumizone plus amitraz combination for the treatment of natural infestations of fleas and/or ticks in client-owned dogs presented as veterinary patients in Europe. This multi-center field clinical study was conducted according to Good Clinical Practice Guidelines (VICH, 2000) in veterinary clinics in Germany and France.

2. Materials and methods

2.1. Animals

Dogs brought to the participating clinics with tick and/or flea infestations were enrolled in the study. To be included in the study, dogs had to have $\geq$3 viable attached ticks and/or $\geq$5 viable fleas. Dogs were not eligible for the study, if they were $<$10 weeks of age, $<$2 kg bodyweight, puppies being nursed, lactating dogs or dogs for which mating was planned. Dogs with any history of apparent reactions to any spot-on parasiticidal treatment, dogs with pre-existing medical or surgical conditions other than tick and/or flea infestation or dogs which were bathed/shampooed within 48 h of treatment or were planned to be bathed/shampooed during the study were also excluded. The animals remained with their owners under their usual housing conditions before, during and after the study.

2.2. Experimental design and methods

Nineteen veterinary clinics in four different areas (North, South, East and West) of Germany and 11 clinics in three areas (Central, West Coast and South) of France enrolled patients to the study. Enrolments were done from May to November 2004, a period when tick and flea infestations regularly occur in these geographical areas of Europe (Beck et al., 2006). Day 0 was defined as the day the animal presented to the clinic was initially identified, assessed and treated. On Day 0, prior to enrolment, the animal's details were recorded, a physical examination was performed to assess the general health of the animal, the suitability of the animal for the study was assessed, the relevant history recorded and the clinical observations including parasite counts on the whole body surface, using a standardized comb-count procedure, were done. Each animal was assigned a unique identification number and informed owner consent was obtained. Ongoing flea and tick challenge was monitored by observing other clients presenting their pets to the clinics during the time of the study.

Dogs infested with $\geq$3 viable attached ticks were selected as tick patients and allocated to treatment group according to a randomization list for tick patients. Dogs with $\geq$5 viable fleas were selected as flea patients and allocated to treatment according to a randomization list for flea patients. Animals were allocated to treatment with metaflumizone plus amitraz or fipronil in the ratio of 2:1. The same animal could be included as both a flea and tick patient if an adequate infestation of both parasites was present at the time of enrolment. Only animals from households with a maximum of four dogs/household or five animals/household (including cats) were considered for enrolment in the study. For tick efficacy, up to three qualifying dogs per household (primary animals) were enrolled. For the evaluation of efficacy in fleas, only one dog per household (primary animal) was enrolled. Other dogs (secondary animals) in the household were treated with the same product as the primary dog. Cats were treated with a registered flea control product. Primary patients were used for efficacy evaluation, while both primary and secondary patients were included in the safety evaluation.

To reduce bias, the study was blinded by using separate personnel to allocate and treat animals (Dispenser), and to conduct the parasite counts and clinical observations (Veterinarian) so that the latter remained blinded to treatment groups.