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A medical drug based on fipronil, dinotefuran, and pyriproxyfen for treatment of ectoparasitic infestations of dogs and cats

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Ectoparasitic infestations of animals are usually treated with drugs based on fipronil, dinotefuran, and pyriproxyfen. That is why, our objective was conducting a field study to assess the efficacy of the drug Profiline Vector (solution for topical use, spot-on application), comparing it with the reference drugs Massive Action Dog Spot-On (drops for topical use, spot-on) and Massive Action Cat Spot-On (drops for topical use, spot-on application) employed against ectoparasite infestations of dogs and cats of different breeds, age, sex, and live body mass. The conducted parasitological studies of the dogs of the experimental and control groups revealed parasitism by the following species: *Ctenocephalides canis* and *Pulex irritans* fleas, with the infestation intensity of 32 to 126 ectoparasites per animal, with an average of 76.9 ± 7.4 parasites per animal; *Trichodectes canis* chewing louse, with the infestation intensity of 7 to 40 ectoparasites per 100 cm^2 of the body surface, with an average of 22.4 ± 3.1 parasites per 100 cm^2 of the body surface; and ticks of the Ixodidae family (*Dermacentor* spp., *Ixodes* spp., *Rhipicephalus sanguineus*), with the tick count of 3 to 13 ectoparasite ticks, accounting on average for 7.4 ± 0.8 ticks per animal. Based on the obtained results, we determined that at the 12th hour after treatment of the dogs with Profiline Vector, its efficacy against flea infestation accounted for 91.2%, and that of the reference drug Massive Action Dog Spot-On was 90.6%. At the 24th hour, the success rate of both drugs was 100%. The efficacy of the tested drug Profiline Vector against Trichodectidae infestation of the dogs accounted for 90.9% on day 7, compared with the 89.9% efficacy produced by the reference drug Massive Action Dog Spot-On; and on days 14 and 21, the efficacy of both drugs equaled 100%. According to the acarological studies, 24 hours after treatment of the dogs with Profiline Vector, its success rate against Ixodidae infestation was 83.3%, compared with 81.6% efficacy exhibited by the reference drug Massive Action Dog Spot-On; at 48th an 72nd hours, both drugs produced 100% efficacy. In the cats of the experimental and control groups, the conducted clinical examination and parasitologic study revealed parasitism by species such as: *Ctenocephalides felis* and *Pulex irritans* fleas, with the parasite count of 20 to 84 ectoparasite insects per animal, with an average of 53.9 ± 5.3 ectoparasites per animal; the eat mite *Otodectos cynotis*, with the intensity of 5 to 16 mites on the surface of the auricle of the animal, and an average infestation intensity of 8.9 ± 0.9 mites per animal. At the 24th hour, Profiline Vector demonstrated 92.1% success rate against flea infestation, compared with 91.2% exhibited by Massive Action Cats Spot-On; at the 48th hour, both drugs were 100 % effective. According to the acarological studies of the cats, Profiline Vector exerted 84.4% efficacy against *Otodectes* infestation on day 7, compared with 83.3% efficacy produced by the reference drug Massive Action Cat Spot-On; on days 14 and 21, the effectiveness of both drugs was 100%. The field trials revealed that the tested drug Profiline Vector applied to the skin of the dogs and cats using the spot-on method in doses recommended by manufacturer was well tolerated by the animals regardless of the breed, age, sex, and body mass, and caused no toxic effect on their organisms, while providing a consistent high efficacy against ectoparasitic infestations.

Keywords: parasitology; spot-on solution; entomoses; acaroses; flea infestation; trichodectiae infestation; ixodidiasis infestation; *Otodectes cynotis*; fipronil; dinotefuran; pyriproxifen; drug efficacy.

Introduction

Ectoparasites, parasites that live on the external surfaces of their hosts, include a broad spectrum of parasitic arthropods that taxonomically belong to the Acari subclass (mites and ticks) and the Insecta class (fleas, chewing and sucking lice, mosquitoes, flies, and the Phlebotominae subfamily of mosquitoes) (ESCCAP, 2018). Ectoparasites can cause direct damages to dogs and cats, including skin lesions and toxicosis (for example, tick paralysis), and with time can provoke reactions of hypersensitivity (for example, flea allergy dermatitis). Blood-feeding ectoparasites (i.e. Acari, fleas, sucking lice, mosquitoes, Phlebotominae, and Triatominae) can cause skin lesions, blood exhaustion, and also be carriers of broad range of microorganisms pathogenic to dogs and cats. Some ectoparasites are intermediate hosts for cestodes (for example, fleas and chewing lice for *Dipylidium caninum*) (www.troccap.com; TroCCAP, 2022).

Over the past several decades, populations of various ectoparasites have grown, and their geographic ranges have expanded. These changes are the result of numerous factors, many of which are anthropogenic, including climate change, fragmentation of the environment, and the existence and presence of hosts. The ranges and populations of ectoparasites are dynamic, and so is the risk of infestations and diseases for dogs and cats (Paddock & Goddard, 2015; Stork, 2018; Salehet al., 2021; Probosteet al., 2024). According to some authors (Thomas et al., 2016; Authoy et al., 2023), increase in domestic and feral animals leads to the spread of ectoparasitic diseases in dogs and cats.

In Ukraine, there have been studies on canine and feline ectoparasites that are currently common in various regions (Kruchynenko, 2020; Yevstafieva & Horb, 2020; Derevianchenko & Petrov, 2023; Melezhyk et al., 2024; Yevstafieva et al., 2024). In European countryes, including Ukraine, flea infestation of companion animals usually varies within 10–45% (Beck et al., 2006; Beugnet & Franc, 2010; Abdullah et al., 2019; Yevstafieva & Horb, 2020), although in some cases there were reported peak indicators of infestation, measuring over 75% (Beugnet & Franc, 2010; Yevstafieva & Horb, 2020). Studies revealed that infestations of dogs and cats by Acari that belong to the Ixodes and Rhipicephalus genera can vary within 30–80% (Claerebout et al., 2013), and those by the ear mite *Otodectes cynotis* range within 14–60% (Sotiraki et al., 2001; Lefkaditis et al., 2009; Melezhyk et al., 2024; Yevstafieva et al., 2024). Infestation by the *Trichodectes canis* chewing louse can occur in dogs of some regions of Europe, especially feral animals (Beugnet et al., 2018). At the same

time, the prevalence of *Trichodectes canis* infestation significantly varies depending on country and category of dogs, ranging 0.2% to 13% (Xhaxhiu et al., 2009; Troyo et al., 2012; Mihalca et al., 2022).

Ectoparasite diseases are a serious health concern for the wellbeing of companion animals and healthcare in general around the world. We cannot fully eliminate the impact of parasites on domestic animals because they have been developing to coexist with host animals for centuries. However, we can decrease the prevalence and spread of those parasites by understanding what factors increase the risk of parasitic diseases and through the use and promotion of effective means of treatment and control. Management of any parasitic infestation of domestic animals depends on thoughtful use of chemotherapeutic drugs for the facilitation of disease and support of wellbeing, as well as on the adherence to hygienic measures for reduction of parasite transmission. The role of integrated programs of combating parasites has increased because the level of antiparasitic resistance is likely to grow (Dantas-Torres et al., 2020; Giannelli et al., 2024).

For treatment of ectoparasitic infestations of dogs and cats, the pharmaceutical market of veterinary drugs offers broadly used insecticides and acaricides from various chemical groups: phenylpyrazoles (fipronil, pyriprole against insects and Acari); chloronicotinyl nitroguanidine (dinotefuran, imidacloprid, nitenpyram against insects); IGR insect growth regulators (pyriproxyfen, S-methoprene, lufenuron against eggs, larvae, and pupas of fleas); isoxazolines (afoxolaner, sarolaner, lotilaner, fluralaner against fleas and Acari); formamidines (amitraz against insects and Acari); macrocyclic lactones and their derivatives (moxidectin, selamectin, milbemycin oxime, eprinomectin against insects and Acari); pyrethroids (permethrin against insects, Acari, and repellent of Acari; flumethrin against Acari; deltamethrin against Acari and as repellent of flying insects); and organophosphates (fenthion, diazinon against insects and Acari) (Wiebe, 2015; Beugnetetal., 2018). All veterinary doctors who prescribe drugs against ectoparasites should document and report any side-effect observed during treatment. Dog owners have many variants of ectoparasiticides for treatment or protection of their pets from infestation with ectoparasites (arthropods). Insecticides and acaricides are usually used spot-on, as solutions, rinses, shampoos, powders, systemic pills, sprays, and collars infused with medications (Beugnet&Franc, 2012; Pfister & Armstrong, 2016; Kruchynenko, 2020).

On the pharmaceutical market of Ukraine, a producer of veterinary drugs offers the drug Profiline Vector (topical solution for spot-on application) for dogs and cats against ectoparasitic infestations. It is based on a combination of fipronil 100 mg / dinotefuran 60 mg / pyriproxyfen 3.0 mg. The drug's combination of active agents – fipronil, dinotefuran, and pyriproxyfen – provides an antiparasitic action toward fleas, chewing lice, lice, ear mites (*Otodectes*), Ixodidae ticks, and blood-sucking dipterans of dogs and cats.

Ectoparasiticide compounds for companion animals can be used for prophylaxis or therapeutically. Noticeable infestations with fleas, lice, or Acari, require treatment to eliminate the parasites. Fortunately, most modern ectoparasiticides have a residual effect and therefore can be used for prophylaxis of re-infestation (Dantas-Torres et al., 2020; Giannelli et al., 2024).

The objective of our study was to perform clinical trials on target animals so as to determine the efficacy of the tested drug Profiline Vector (topical solution for spot-on application), comparing it with the reference drugs Massive Action Dog Spot-On and Massiv Action Cat Spot-On (drops for topical application via spot-on), which are based on a combination of fipronil, dinotefuran, and pyriproxyfen, used in doses recommended by manufacturer.

Materials and methods

In the studies, we used dogs and cats of different breeds, age, sex, live body mass, which had been spontaneously infested with ectoparastites: the fleas *Ctenocephalides canis*, *C. felis*, and *Pulex irritans*; the chewing louce *Trichodectes canis*; a Sarcoptidae mite *Otodectes cynotis*; and the Ixodidae ticks (*Dermacentor* spp., *Ixodes* spp., *Rhipicephalus sanguineus*). The research was conducted in veterinary clinics in Lviv, considering the animals from pet owners and volunteers.

For clinical parasitological studies, according to the analogue principle, we formed an experimental and control group for each kind of parasite, with seven animals in each. To treat parasitic infestations of the animals (dogs and cats) of the experimental groups, we used the tested drug Profiline Vector (solution for external spot-on application), and the dogs and cats of the control groups were treated with the reference drugs Massive Action Dog and Massive Action Cat, respectively (drops for topical spot-on application). The drugs were used topically, directly on the dry skin in the region unavailable for licking, in doses recommended by manufacturer. In cases of *Otodectes* in cats, the auricle and the ear canal were previously cleared of dry earwax, exudates, and scabs. The drug was used singly, 2–3 drops in each ear (the drops were administered to both ears of the animal). For even distribution of the drug, the auricle was folded in half and slightly massaged at the base. The residue of the drug from the used pipette (in calculation per body mass of the animal) was applied onto the skin between the shoulder blades. To prevent sprinkling of the drug, the animal's head was fixated for several minutes. All the animal groups were monitored around the clock.

Following our objectives, we conducted parasitological studies of the animals using the metod of visual examination and collected samples for laboratory studies to detect arthropods according to the clinical practice of the European Agency (VICH GL9 Animal GCP) and scientific recommendation of the World Association for the Advancement of Veterinary Parasitology (WAAVP) regarding assessments of the efficacy of parasiticides for treatment, prophylaxis, and control of ectoparasite infestations of dogs and cats (Marchiondo et al., 2007, 2013; Otranto et al., 2021).

The intensity of infestation by the fleas *Ctenocephalides canis*, *C. felis*, and *Pulex irritans* was assessed by counting ectoparasites on the animals' coat through grooming with a fine-tooth comb across five anatomical regions: the dorsal median line (linea dorsalis medianum), ischial tuberosity (tuberis chiadicum), the left side (pars lateralis sinister "left"), the right side (pars lateralis dexter "right"), and inguinal region (regio inguinalis). The grooming usually lasted between 5 and 20 minutes in dogs and about 7 minutes in cats (Dryden et al., 1994; Marchiondo et al., 2007). The intensity of infestation by the chewing lice *Trichodectes canis* was determined by grooming the coat with a comb and visually counting the ectoparasites in 3–4 regions of the body, accounting for the general area of 100 cm^2 (Woldstad et al., 2014).

Acari infestations of the animals were diagnosed visually and through analysis of sampled material. By the means of bilateral otoscopy, we detected live Sarcoptidae mites of *O. cynotis* on the internal surface of the auricle and the ear canal of the cats (Combarros et al., 2019). The intensity of infestation with *O. cynotis* was determined by counting ectoparasites on the superficial ear smears taken from the affected animals during microscopical examination (visual method) (Beugnet et al., 2018; Zajac et al., 2021). The Ixodidae ticks were collected from the animal bodies in a cuvette. The dogs were restrained, and their coats were inspected starting from the head, then the neck, back, sides, stomach, and limbs. During the examination, the hair was groomed as needed. First, we examined the patients with the naked eye, and later using an otoscope. The detected Ixodidae ticks were removed from the skin using tweezers or manually with a rubber glove (trying not to crush them) with slight side-to-side shaking to remove the proboscis undamaged. The larvae and nymphs were removed with tweezers (Hendrix & Robinson, 2017; Beugnet et al., 2018).

The collected ectoparasites were identified microscopically according to practical guidelines (Hendrix & Robinson, 2017; Beugnet et al., 2018; Zajac et al., 2021).

The drugs' efficacy against animal ectoparasites in each group was evaluated using the Abbott's formula (Marchiondo et al., 2007, 2013; Yevstafieva et al., 2021, 2023; Yuskiv et al., 2024). Following the treatment of the animals, the drugs' efficacy against flea infestation was assessed on the 12th, 24th, and 48th hours and effectiveness against *Trichodectes* infestation was examined on days 7, 14, and 21. These evaluations involved grooming the animals with fine-tooth combs and thoroughly examining their coats for the presence of wingless ectoparasitic insects. In cases of *Otodectes* and Ixodidae

infestations, the parasite viability in the experimental and control groups was examined on days 7, 14, and 21 after treatment; and for Ixodidae ticks (*Dermacentor* spp., *Ixodes* spp., *Rhipicephalus sanguineus*), the inspection was carried out at the 24th, 48th, and 72nd hours after treatment.

All the procedures described in the study were performed according to the European Directive (Directive 2010/63/ES) on procedures for protection of animals used for scientific purposes.

The analysis of the obtained data was conducted using the Statistica 6.0 software (StatSoft Inc., USA). The data are presented in tables as x ± SD (mean value ± standard deviation). The differences between the values in the control and experimental groups were determined using ANOVA, where the differences were considered significant at $P < 0.05$ (taking into account the Bonferroni's correction).

Results

During the clinical examination and parasitological study of the dogs and cats of different breeds, sex, live body mass, admitted to the veterinary clinics, from pet owners and volunteers, we diagnosed infestation with causative agents of entomiases and acariases, namely: *Ctenocephalides canis*, *C. felis*, *Pulex irritans* (fleas), *Trichodectes canis* (chewing lice), *Otodectes cynotis* (Sarcoptiformes mites), *Dermacentor* spp., *Ixodes* spp., and *Rhipicephalus sanguineus* (Parasitiformes mites).

Grooming of the dogs with a fine-tooth comb for the established time in five anatomical regions on each animal, we detected infestation by the fleas *C. canis* and *P. irritans* with the intensity of 32 to 126 fleas per animal, an average of 76.9 ± 7.4 ectoparasite insects per animal. Those dogs were divided into two groups – experimental and control – consisting of seven animals each. In the experimental group, the infestation intensity accounted for 32 to 126 fleas per animal, with an average of 77.7 ± 12.2 ectoparasites per animal, and in the control group the infestation intensity was 42 to 116 fleas per animal, with an average of 76.1 ± 9.6 ectoparasite insects per animal (Table 1). The animals were observed suffering from itching and scratched incessantly.

The experimental-group dogs were treated with Profiline Vector, and the control group of the dogs with the reference drug Massive Action Dog Spot-On according to manufacturer's recommendations (taking into account the animals' live body mass, and therefore the required dose of the drug, mL). The patients were later examined at the 12th, 24th, and 48th hours: the coat was inspected for live ectoparasite insects, noting the general condition, behavior, appetite, and body temperature.

Table 1
Efficacy of Profiline Vector and the reference drug Massive Action Dog Spot-On against flea infestation (x ± SD, n = 7)

Infestation intensity, species of fleas on the bodies of animals	Prior to treatment	After treatment			Efficacy, %		
		12 h	24 h	48 h	12 h	24 h	48 h
Experimental group, Profiline Vector	77.7 ± 12.2	6.9 ± 1.1	0.0	0.0	91.2	100.0	100.0
Control group, Massive Action Dog Spot-On	76.1 ± 9.6	7.1 ± 0.9	0.0	0.0	90.7	100.0	100.0

Treatment of both the experimental-group dogs with the tested drug Profiline Vector and the control-group dogs with the reference drug Massive Action Dog Spot-On produced good therapeutic results. Thus, in the experimental group, at the 12th hour, the intensity of infestation by the fleas *C. canis* and *P. irritans* decreased to 3 to 11 ectoparasite insects per animal, with an average of 6.9 ± 1.1 ectoparasite insects per animal, whereas in the control group the infestation intensity by *C. canis* and *P. irritans* decreased to 4 to 11 ectoparasite insects per animal, with an average of 7.1 ± 0.9 ectoparasite insects per animal. Starting from the 24th hour and at the 48th hour after treatment, the entomological studies revealed complete absence of *C. canis* and *P. irritans* on the coats of the dogs of both groups (Table 1).

Therefore, in cases of spontaneous flea infestation of the dogs, the tested drug Profiline Vector demonstrated 91.2% efficacy at the 12th hour after treatment, while the efficacy of the reference drug Massive Action Dog Spot-On equaled 90.6%. At the 24th and 48th hours after treatment of the dogs (of different breeds, age, sex, live body mass), 100% effectiveness against the Siphonaptera infestation was exhibitted by both drugs (Table 1).

As a result of the conducted clinical examination and entomological study of the dogs by grooming revealed parasitism by the chewing louse *T. canis*, with the infestation intensity of 7 to 40 ectoparasites per 100 cm² of the body surface, with an average of 22.4 ± 3.1 ectoparasite insects per 100 cm² of the body surface. Those dogs were divided into two groups (experimental and control), seven animals in each. In the experimental-group dogs, the intensity of infestation by *T. canis* accounted for 9 to 38 ectoparasites per 100 cm² of the body surface, with an average of 22.0 ± 4.6 ectoparasites per 100 cm² of the body surface, and in the control-group dogs it ranged 7 to 40 ectoparasites per 100 cm² of the body surface, with an average of 22.7 ± 4.6 ectoparasite insects per 100 cm² (Table 2). The clinical signs of *T. canis* infestation included skin irritation, scratches resulting in scabs, dermatitis, and itching.

Table 2
Efficacy of Profiline Vector and the reference drug Masive Action Dog Spot-On against *Trichodectes canis* (x ± SD, n = 7)

Infestation intensity, *Trichodectes canis* on the bodies of animals	Prior to treatment	After treatment			Efficacy, %		
		day 7	day 14	day 21	day 7	day 14	day 21
Experimental group, Profiline Vector	22.0 ± 4.6	2.0 ± 0.4	0.0	0.0	90.9	100.0	100.0
Control group, Massive Action Dog Spot-On	22.7 ± 4.6	2.3 ± 0.4	0.0	0.0	89.9	100.0	100.0

According to the results of entomological studies of the dogs, we determined that both the tested drug Profiline Vector and the reference drug Massive Action Dog Spot-On reduced the intensity of infestation by the ectoparasite *T. canis*. In the experimental-group animals, on day 7 of the experiment, the louse count decreased to 1 to 3 ectoparasites per 100 cm² of the body surface, with an average of 2.0 ± 0.3 ectoparasite insects per 100 cm² of the body surface. At the same time, following the treatment of the control-group dogs with the reference drug according to manufacturer's recommendations, on day 7 of the experiment, the intensity of infestation by *T. canis* was 1 to 4 ectoparasites per 100 cm² of the body surface, with an average of 2.3 ± 0.4 ectoparasite insects per 100 cm² of the body surface. During the clinical examination and entomological study on days 14 and 21 post-treatment, we observed no live *T. canis* individuals in either the control or experimental groups (Table 2). Therefore, the obtained results indicate that on day 7 after application, the tested drug Profiline Vector produced 90.9% efficacy against Trichodectidae infestation, whereas the reference drug Massive Action Dog Spot-On exhibited 89.9% efficacy. On days 14 and 21 after treating the dogs, the efficacy against Trichodectidae infestation was 100% for both drugs (Table 2).

The results we obtained suggest that the drug that we tested according to manufacturer's recommendations on the dogs in field studies displays notable activity toward the wingless ectoparasites *C. canis*, *P. irritans*, and *T. canis*.

By examining the coats of the dogs on the head, neck, back, sides, stomach, and limbs, we found parasitism by ticks of the Ixodidae family (*Dermacentor* spp., *Ixodes* spp., *Rhipicephalus sanguineus*), with the tick count of 3 to 13 ectoparasites per animal and an average

of 7.4 ± 0.8 ectoparasite ticks per animal. Those dogs were divided into two groups (experimental and control), seven in each. In the experimental-group dogs, the intensity of the Ixodidae infestation was 4 to 13 ectoparasites per animal, with an average of 7.7 ± 1.2 ectoparasite ticks per animal, whereas in the control-group dogs the intensity of Ixodidae infestation accounted for 3 to 11 ectoparasites per animal, with an average of 7.0 ± 1.0 ectoparasite ticks per animal (Table 3).

According to the results of acarological study of the dogs, at the 24th hour after using the tested drug Profiline Vector and the reference drug Massive Action Dog Spot-On, the number of the Ixodidae ticks decreased to 1 to 2 ectoparasites per animal, with an average of 1.3 ± 0.2 ectoparasite ticks per animal in both groups. During the acarological studies at the 48th and 72nd hours after applying the drugs on the coats, no Ixodidae ticks (*Dermacentor* spp., *Ixodes* spp., *Rh. sanguineus*) were found in both groups of the dogs (Table 3).

Table 3

Efficacy of Profiline Vector and the reference drug Massive Action Dog Spot-On against Ixodidae (x ± SD, n = 7)

Infestation intensity, Ixodidae on the bodies of animals	Prior to treatment	After treatment			Efficacy, %		
		24 h	48 h	72 h	24 h	48 h	72 h
Experimental group, Profiline Vector	7.7 ± 1.2	1.3 ± 0.2	0.0	0.0	83.1	100.0	100.0
Control group, Massive Action Dog Spot-On	7.0 ± 1.0	1.3 ± 0.2	0.0	0.0	81.4	100.0	100.0

Thus, we determined that by the 24th hour after treatment, the studied drug Profiline Vector decimated 83.1% of the Ixodidae ticks on the dogs, while the success rate of the reference drug Massive Action Dog Spot-On was 81.4%, and at the 48th and 72nd hours the efficacy of both drugs was 100% (Table 3). The results we obtained suggest that the tested drug used according to manufacturer's recommendations on the dogs of different breeds, age, sex, and live body weight in field study exerts notable acaricidal activity toward the Ixodidae ticks (*Dermacentor* spp., *Ixodes* spp., *Rh. sanguineus*).

As a result of the conducted clinical examination and parasitological study of the cats by grooming using a fine-tooth comb, we determined parasitism by the fleas *C. felis* and *P. irritans* with the infestation intensity of 20 to 84 fleas per animal, with an average of 53.9 ± 5.3 ectoparasite insects per animal. Those animals were divided into two groups (experimental and control), seven animals each. In the experimental group, the flea count was 23 to 84 fleas per animal, with an average of 54.3 ± 8.0 ectoparasite insects per animal, and the infestation intensity in the control group accounted for 20 to 76 fleas per animal, with an average of 53.6 ± 7.6 ectoparasite insects per animal (Table 4). The animals suffered from itching and had inflammation-caused skin thickening.

Table 4

Efficacy of Profiline Vector and the reference drug Massive Action Cat Spot-On against Siphonaptera infestations of the cats (x ± SD, n = 7)

Infestation intensity, fleas on the bodies of animals	Prior to treatment	After treatment		Efficacy, %	
		24 h	48 h	24 h	48 h
Experimental group, Profiline Vector	54.3 ± 8.0	4.3 ± 0.7	0.0	92.1	100.0
Control group, Massive Action Cat Spot-On	53.6 ± 7.6	4.7 ± 0.7	0.0	91.2	100.0

The experimental-group cats were treated with the tested drug Profiline Vector, whereas in the control group we used the reference drug Massive Action Cat Spot-On according to manufacturer's recommendations (taking into account the animal's body mass, thus selecting the dose in mL). At the 24th and 48th hours of the experiment, we conducted the following examinations: inspection of the coats for vital ectoparasite insects, and assessment of the general condition, appetite, and measurement of the body temperature.

After treating the experimental-group cats with the tested drug Profilne Vector and the control-group cats with the reference drug Massive Ation Cat Spot-On, we observed a decrease in the flea counts. Thus, in the experimental group, at the 24th hour, the intensity of infestation by the fleas *C. felis* and *P. irritans* decreased to 2 to 7 ectoparasite insects per animal, with an average of 4.3 ± 0.7 ectoparasite insects per animal, while in the control group, at the 24th hour, the intensity of infestation by *C. felis* and *P. irritans* also decreased to 2 to 7 ectoparasite insects per animal, with an average infestation intensity of 4.7 ± 0.7 ectoparasite insects per animal. At the 48th hour after treatment, the entomological studies found no fleas *C. felis* or *P. irritans* on the animals in either group (Table 4). Therefore, the obtained results indicate that at the 24th hour after using Profiline Vector, its efficacy toward flea infestation accounted for 92.1%, as compared with 91.2% produced by Massive Action Cat Spot-On. At the 48th hour after treating the cats (of different breeds, age, sex, live mass), both drugs were 100% effective against Siphonaptera infestation (Table 4).

As a result of the conducted clinical analysis and parasitological study, the cats were found to have symptoms of otitis and dermatitis of the outer ear. The main signs of otitis were itching, reddening of the auricle, exudations in the ear canal, and also the ill animals tilted their heads to the side of affected ear. At the same time, the cats were observed to be infested by the ear mite *O. cynotis*, with the infestation intensity of 8.9 ± 0.9 mites per animal. These animals were divided into two groups (experimental and control), seven individuals each. In the experimental group, prior to application of the tested drug, the intensity of *O. cynotis* infestation accounted for 5 to 13 mites on the internal surface of the auricle, with an average of 8.3 ± 1.0 mites per animal. In the control-group cats, before treatment, the intensity of *O. cynotis* infestation accounted for 5 to 16 mites on the internal surface of the auricle, with an average of 9.4 ± 1.5 mites per animal (Table 5).

Table 5

Efficacy of the drug Profiline Vector and the reference drug Massive Action Cat Spot-On against *Otodectes* infestation of the cats (x ± SD, n = 7)

Intensity of infestation with *Otodectes cynotis* mites in the ears of animals	Prior to treatment	After treatment			Efficacy, %		
		day 7	day 14	day 21	day 7	day 14	day 21
Experimental group, Profiline Vector	8.3 ± 1.0	1.3 ± 0.2	0.0	0.0	84.3	100.0	100.0
Control group, Massive Action Cat Spot-On	9.4 ± 1.5	1.6 ± 0.3	0.0	0.0	83.0	100.0	100.0

In the experimental group, on day 7 after treatment with Profiline Vector, the number of Otodectos cynotis declined to 1-2 mites, with an average of 1.3 ± 0.2 mites per animal. In the control group, on day 7 after treatment with Massive Action Cat Spot-On, the number of Otodectos cynotis in the cats' ears decreased to 1–3 mites, with an average of 1.6 ± 0.3 mites per animal. The acarological study of the animals on days 14 and 21 after treatment revealed no *O. cynotis* on the auricle surface in both groups (Table 5).

Thus, the obtained data indicate that on day 7 after using Profiline Vector in doses recommended by manufacturer, its efficacy against feline otodectosis was 84.4%, as compared with 83.3% produced by Massive Action Cat Spot-On. On days 14 and 21 after treating the animals (different breeds, age, sex, live body mass), both drugs produced 100% efficacy against Otodectes (Table 5).

According to the data of the general clinical observations, no side-effects were observed from the tested drug Profiline Vector and

the reference drugs Massive Action Dog Spot-On and Massive Action Cat Spot-On, used against Siphonaptera, Trichodectidae, Ixodidae, and *Otodectes* infestations in cats and dogs.

In *in vivo* conditions, after treating the coats singly in the regions where the animals could not reach to lick, Profiline Vector exerted 100% insecticidal and acaricidal actions toward wingless insects such as fleas, chewing lice, Sarcoptoidea mites, parasitoform ticks that infest cats and dogs, and caused no skin irritation, dermatitis, seborrhea, allergic, or other undesirable effects.

Discussion

The new composition of the veterinary drug, containing active compounds such as fipronil, dinotefuran, and pyriproxyfen, used locally via spot-on on the dogs and cats (Profiline Vector), was safe and highly effective against natural infestation by fleas, chewing lice, Ixodidae ticks, and *Otodectes* mites.

Pour-on or spot-on drugs are particularly convenient medications. Local application for local or systemic effects often confers additional advantages such as reduction of stress for the animals and facilitated administration compared with peroral delivery and injections. Usually, the application is performed at one spot (hence the name), but sometimes several points are required for an optimal distribution on the animal, or an adjusted dose. In some cases, drugs retain on the hair, skin fatty glands of the animals, hair follicules (for example, fipronil, pyriproxyfen), and deepen with time, forming "depots" in the derm, from which they are gradually released over a certain period, thus providing a prolonged action of the drug. Depending on the degree of absorption and fat-dermal blood circulation, different compositions of medical preparations provide action ranging couple weeks to several months. Insectoacaricides, which spread from the application sites, are usually effective upon contact with ectoparasites, although in some cases, blood is required to deliver lethal dose (Boy et al., 2000). The most common and representative compositions for spot-on application to companion animals are: fipronil (10%, w/v); fipronil (9.8%, w/v), and methoprene (8.8%, w/v); dinotefuran (4.95%, w/v), permethrin (36.08%, w/v), and pyriproxyfen (0.44%, w/v); permethrin (45%, w/v); permethrin (65%, w/v); permethrin (45%, w/v), and pyriproxyfen (5%, w/v); amitraz (7.6%, w/v), fipronil (6.4%, w/v), and methoprene (5.8%, w/v); indoxacarb (13.01%, w/v), and permethrin (42.5%, w/v); indoxacarb (19.53%, w/v), and imidacloprid (9.1%, w/v); imidacloprid (10%, w/v), and permethrin (50%, w/v); imidacloprid (8.8%, w/v), and permethrin (44%, w/v); methoprene (2.3%, w/v), and phenotrin (85.7%, w/v); amitraz (15%, w/v), and metaflumizone (15%, w/v); metaflumizone (9.1%, w/v); cyflutrin (1%, w/v); emodepside (1.98%, w/v), and praziquantel (7.94%, w/v); selamectin (6%, w/v), or (12%, w/v); selamectin (6%, w/v), and сароланер (1%, w/v); esafoxolaner (1.2%, w/v), eprinomectin (0.4%, w/v), praziquantel (8.3%, w/v); moxidectin (0.5%, w/v), and other compositions (Lavy et al., 2022).

The efficacy of the tested composition with the active agents fipronil (10%; w/v, solution) /dinotefuran (6%; w/v, solution) /pyriproxyfen (0.3%; w/v, solution) was not inferior to the composition of dinotefuran (22%; w/v, solution) /pyriproxyfen (3%; w/v, solution), or the composition of dinotefuran (4.95%; w/v, solution) /pyriproxyfen (0.44%; w/v, solution) / permethrin (36.08%; w/v, solution), or the composition of fipronil (9.8%; w/v, solution) /(S)-methoprene (11.8%; w/v, solution), used locally spot-on against fleas and Acari, respectively (Dryden et al., 2011).

Furthermore, the efficacy of the new spot-on formula of fipronil / dinotefuran / pyriproxyfen against fleas was also confirmed in the studies assessing the efficacy of a local ectoparasiticide spot-on ointment containing 4.95% dinotefuran (w/v), 0.44% pyriproxyfen (w/v), and 36.08 % permethrin (w/v) (Vectra 3D™) against a French strain of the flea *Ctenocephalides canis* and a Portuguese strain of the dipteran *Phlebotomus perniciosus* in dogs (Liénard et al., 2013).

In present study, we determined that after treating the dogs with the tested drug Profiline Vector, at the 12th hour, 91.2% of the fleas were killed, compared with 90.7% success rate of the reference drug Massive Action Dog Spot-On; and at the 24th hour, both drugs demonstrated 100% efficacy. At the same time, fast action of neonicotinodes (dinotefuran) and elimination of the fleas is especially beneficial compared with the slower adulticides such as selamectin and fipronil (Baynes, 2018). The studies by Stanneck et al. (2003) revealed that pyriproxyfen impairs the synthesis of chitin of the larvae, disrupts their moulting, hinders the development of pupae, and causes death of the insects in preimago development phases, thus ceasing the replenishment of the ectoparasite populations. It was found that pyriproxyfen sterilized fleas for six hours after being applied at a concentration of 0.01 mg/kg to the cat coat (Meola et al., 2000; Stanneck et al., 2003). Pyriproxyfen is often applied spot-on and is effective against eggs of fleas in cats for 56 days (Rust, 2005). This insect growth regulator (IGR) was tested in a minimal dose of 10 mg/kg of body mass twice with three-month interval between the doses. The result was that it significantly diminished the flea population. Moreover, on day 180, the percentage of "zero-flea" cats increased up to 88%. Therefore, local application of pyriproxyfen in the corresponding period offers a way of combating fleas in domestic conditions (Maynard et al., 2001).

The parasitological studies revealed that following treatment of cats with the tested drug Profiline Vector and the reference drug Massive Action Cat Spot-On, at the 24th hour, their efficacy against Siphonaptera infestation accounted for 92.1% and 91.2%, respectively, with both drugs demonstrating 100% effectiveness at the 48th hour. Fast elimination of fleas was also observed after treating cats with the drugs Vectra for Cats, Vectra for Cats and Kittens, Vectra for Dogs and Puppies, because those products are applied spot-on and their active agents are dinotefuran and pyriproxyfen. Those medical drugs kill fleas in 6 hours and are used each month for control of adult fleas and all immature stages of fleas, including eggs, larvae, and pupas. Those are some of the safest and most effective agents in complex therapy against flea allergic dermatitis (FAD) (Wakita et al., 2005).

Fipronil is a reputable insecticide and acaricide. This compound acts toward insects and Acari, blocking the action of gamma-aminobutyric acid. It also acts through a contact, and because it accumulates in the skin and fat glands it remains active against fleas and Acari for at least four weeks (Dryden, 2009; Baynes, 2018). Fipronil was observed to be as effective as selamectin and imidacloprid in reduction of the intensity of infestation by *Ctenocephalides felis* in the dogs that were kept in a flea-infested environment for three months (Dryden et al., 2000; Ritzhaupt et al., 2000). The clinical trials have confirmed that a combination of dinotefuran and fipronil in one drug exerted a stronger synergic insecticidal action against *C. felis* in *in vitro* experiments. A rapid insecticidal effect was observed as early as three hours after application, and also six hours after re-infestation that occurred six weeks after the initial treatment. Because of their insecticidal activities, a combination of dinotefuran and fipronil can be considered reliable against ectoparasites for protection of cats from flea infestation and accompanying diseases (Delcombel et al., 2017).

The results of the field studies revealed that after treatment of the dogs with the tested drug Profiline Vector, on day 7, its efficacy against Trichodectidae infestation was 90.9%, while the reference drug Massive Action Dog Spot-On produced 89.9% efficacy; on days 14 and 21, the efficacy of both drugs equaled 100%. The medical drugs Frontline® Spray (0.25% fipronil, w/v), Frontline® Spot-On for Dogs (10% fipronil, w/v), and Frontline® Plus for Dogs (10% fipronil, w/v and 9% (S)-methoprene, w/v) are also effective against the chewing louse *Trichodectes canis*. Thus, the efficacy of the drugs against this species accounted for > 98% on day 2 and 100% on days 28 and 42 in all the treated groups of animals. The results of the studies demonstrate that fipronil for local application is effective for treatment and control of infestation by the chewing louse *T. canis* in dogs (Pollmei er al., 2002).

The results of this study indicate that Profiline Vector and Massive Action Dog Spot-On have notable acaricidal actions, producing 83.1% and 81.4% efficacy against Ixodidae at the 24th hour, respectively. At 48th and 72nd hours, both drugs were 100% effective. We should note that the drugs Effipro® Spot-On and Frontline® Topspot, which are 10% (w/v) solutions for spot-on application based on fipronil, differ by some of their carriers. However, despite different carriers, the two formulas provide a similar protection from infesta-

tion by the mite *Ixodes ricinus* and are well tolerated by the animals. At the same time, the two medical forms of fipronil exerted 94% and 99% efficacy against *I. ricinus*, respectively. Both forms of fipronil prevented new infestations for five weeks (Effipro®) and three weeks (Frontline®), with an efficacy of > 90% when studying 48 h after treatment (Bonneau et al., 2010).

Some reports note that fipronil is effective against otoacariasis caused by the ear mite *Otodectes cynotis* (Ghubash, 2006). The drugs presented in the study – Profiline Vector and Massive Action Cat Spot-On with the composition of active agents fipronil / dinotefuran / pyriproxyfen – produced 84.3% and 83.0% efficacy against feline *Otodectes* infestation on day 7, respectively, and both produced 100% on days 14 and 21. The monodrug Insectostop for dogs and cats containing fipronil (10%, w/v) as active agent – when used individually, topically spot-on, singly – was effective against the fleas *Ctenocephalides canis*, *C. felis*, *Pulex irritans*, and Ixodidae ticks *Ixodes ricinus*, *Dermacentor reticulatus*, and *Otodectes cynotis*. Following application of the monodrug against flea infestation of the dogs and cats, the efficacy was 87.9% to 92.4% at the 8th hour of the experiment and 100% on the first and third days. Clinical studies also revealed that using the monodrug against canine Ixodidae decreased the infestation by 82.9% at the 8th hour, and 97.6% and 100% at the 24th and 72nd hours, respectively. Against *Otodectes* infestation of the dogs and cats, the monodrug's efficacy measured 75.6% to 76.9%, on day 7 and 98.1% to 100% on days 14 and 21 (Tishyn et al., 2021).

In field conditions, dogs and cats are frequently vulnerable to re-infestation by ectoparasites: fleas, chewing and sucking lice, and ticks and mites in the environment. Therefore, ectoparasiticides must provide consistent effectiveness throughout the entire treatment period in order to protect the animals from re-infestation. It is necessary not only for alleviation of immediate clinical impact of those ectoparasites on the infested animals, but is also important to help decrease the transmission of pathogens due to the direct clinical significance for populations of dogs and cats, and to disrupt the epizootologic cycle of these pathogens. The new composition for spot-on application containing fipronil, dinotefuran, and pyriproxyfen (Profiline Vector) for dogs and cats in doses recommended by manufacturer provides high and stable efficacy against natural infestation by fleas, chewing lice, Ixodidae ticks, and *Otodectes* mites, which was confirmed by the clinical (field) studies.

Conclusions

The parasitological studies revealed that the tested drug Profiline Vector (solution for topical spot-on application) for dogs and cats is a highly effective insecticide against the ectoparasite fleas *Ctenocephalides canis*, *C. felis*, *Pulex irritans*, wingless chewing louse *Trichodectes canis*; and also a highly successful acaricide against the mite *Otodectes cynotis* and parasitoform ticks of the Ixodidae family (*Dermacentor* spp., *Ixodes* spp., *Rhipicephalus sanguineus*).

When determining the therapeutic effectiveness of Profiline Vector for dogs and cats against entomiases and acariases after single spot-on application in doses recommended by manufacturer, it was well tolerated by the animals regardless of breed, age, sex, body mass, and caused no toxic impact on the animals, while providing high efficacy against natural ectoparasite infestations.

The authors declare that there is no conflict of interest.

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