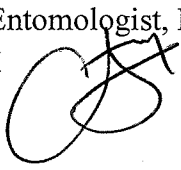


Efficacy Review

Date: December 6, 2010

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 12-6-10

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Products: Sergeant's Fipronil + Cyphenothrin Squeeze-on for Dogs

EPA Reg. #: 2517-RUN

A.I.'s: Fipronil (9.8%), Cyphenothrin (5.0%)

Decision #s: 435798

DP #s: 380757

Submission: R310, New Products, RD Science Review

MRIDs: Submitted: 48129609, 48129610, 48129611, 48129612, 48129613

Cited: 43121114, 43121115, 43121116, 43121117, 43121118,
43121122, 43577712, 45620501, 45620502, 45620503,
45620504, 45620505, 45620506, 45628201

GLP: No

MRID 48129609

Title: Overview and Summary of Fipronil/Cyphenothrin Dog Efficacy for Sergeant's Fipronil + Cyphenothrin Squeeze-On for Dogs (Overview of other submissions).

Guideline: OPPTS 810.3300

Study Summary of the Results:

This submission is an overall summary and clarification of the other submitted MRIDs associated with this application

Entomologist's Observations/Discussion:

Supplementary Information

MRID 48129810

Title: Immediate Efficacy of a Combined Application of Frontline Plus with Cyphenothrin as a Squeeze-on against Fleas (*Ctenocephalis felis*) and Ticks (*Rhipicephalus sanguineus*) on Dogs.

Guideline: OPPTS 810.3300

Materials and Methods: Cyphenothrin was added to Frontline plus at 3 rates (5%, 10%, and 15%) for efficacy evaluations. Dose volumes applied were based on the Frontline label, but dilution was not taken into account for the existing fipronil, therefore fipronil dosage was slightly lower than that of Frontline alone. 18 dogs were allocated to 6 groups of 3 dogs each. Group 1, untreated control; Group 2, Frontline alone, Groups 3-5 Frontline plus cyphenothrin at described rates. Dogs were infested with 100 fleas and 50 ticks one day before treatment, and again at 7 and 14 days after treatment. Counts were made at 1 and 4 hours post treatment and also on day 14 at 1 and 4 hours post placement—this was to measure speed of kill and/or repellency. Counts were also made at 24 and 48 hours after initial infestation and all re-infestations. Parasites were not removed until the final count. Mortality was calculated using Abbott's formula. For speed of kill/repellence, the number of killed/repelled fleas on the liner below each treated dog was divided by the total number of fleas placed on the dog (all x 100), adjusted for 'normal' attrition on control dogs.

Study Summary of the Results:

1. Mean efficacy against fleas and ticks exceeded 90% when assessed at 1-2 days after treatment or reinfestation with parasites, through 14 days after treatment.
2. Immediate efficacy on fleas (i.e. kill/repellence within 4 hours of treatment) ranged from 9-74% for 1-4 hours immediately after treatment. With reinfestations after 14 days from treatment, efficacy exceeded 99% within 4 hours for all treatments that included cyphenothrin.
3. Immediate efficacy on ticks ranged from 2-64% for 1-2 hours immediately after treatment. With reinfestations after 14 days from treatment, efficacy exceeded 95% within 1 hour, for the lowest percentage of cyphenothrin treatment, and exceeded 84% for all treatments.

Entomologist's Observations/Dicussion:

1. Efficacy against fleas and ticks was adequate to support controls claims through 14 days after treatment.
2. While immediate efficacy against fleas and ticks was enhanced when assessed at 1 and 4 hours after treatment (or reinfestation), the immediate efficacy did not exceed 90% with any consistency for the treatments evaluated immediately after treatment. However, after 14 days, this immediate efficacy was observed for reinfestations of both fleas and ticks. This is likely due to the more complete spread of the spot-on material throughout the animal coat at 14 days. Claims for killing (or 'starts killing') within hours would be supported by this data, but not immediately after treatment of the animals.

MRID 48129811

Title: Immediate Efficacy Following Application of Frontline with Cyphenothrin Squeeze-on against Fleas (*Ctenocephalis felis*) and Ticks (*Rhipicephalus sanguineus*) on Dogs.

Guideline: OPPTS 810.3300

Materials and Methods: Cyphenothrin was added to Frontline plus at the rate of approximately 5% (4.76% cyphenothrin) for efficacy evaluations. Dose volumes applied were based on the Frontline label, but dilution was not taken into account for the existing fipronil, therefore fipronil dosage was slightly lower than that of Frontline alone. 18 dogs were allocated to 3 groups of 6 dogs each. Group 1, untreated control; Group 2, Frontline+cyphenothrin, Groups 3, Frontline alone.. Dogs were infested with 100 fleas and 50 ticks one day before treatment, and again at 7, 14, 21, and 28 days after treatment. Counts were made at 1 and 4 hours post treatment and also after every reinfestation—this was to measure speed of kill and/or repellency. Counts were also made at 24 and 48 hours after initial infestation and all re-infestations. Parasites were not removed until the final count. Mortality was calculated using Abbott's formula. For speed of kill/repellence, the number of killed/repelled fleas on the liner below each treated dog was divided by the total number of fleas placed on the dog (all x 100), adjusted for 'normal' attrition on control dogs.

Study Summary of the Results:

1. Mean efficacy against fleas and ticks exceeded 90% when assessed at 1-2 days after treatment or reinfestation with parasites, through 28 days after treatment.
2. Immediate efficacy on fleas (i.e. kill/repellence within 4 hours of treatment) ranged from 9-68% for 1-4 hours immediately after treatment. With reinfestations after 7, 14, 21, and 28 days from treatment, efficacy exceeded 90% within 4 hours for all treatments that included cyphenothrin, but did not exceed 90% within 1 hour after reinfestation.
3. Immediate efficacy on ticks ranged from 5-75% for 1-2 hours immediately after treatment. With reinfestations after 7, 14, 21, and 28 days from treatment, efficacy exceeded 90% within 4 hours for all dates. For 21 and 28 days from treatment, adequate efficacy was observed within 1 hour of reinfestation.

Entomologist's Observations/Dicussion:

1. Efficacy against fleas and ticks was adequate to support controls claims through 28 days (one month) after treatment.
2. While immediate efficacy against fleas and ticks was marginally enhanced when assessed at 1 and 4 hours after treatment (or reinfestation), the immediate efficacy did not exceed 90% with any consistency for the treatments evaluated immediately after treatment. However, after 7 days, this immediate efficacy was observed for reinfestations of both fleas and ticks. This is likely due to the more complete spread of the spot-on material throughout the animal coat at 7+ days. Claims for killing (or

'starts killing') within hours would be supported by this data, but not immediately after treatment of the animals.

MRID 48129812

Title: Immediate Efficacy Following Application of Frontline Plus with Cyphenothrin Squeeze-on against Fleas (*Ctenocephalis felis*) and Ticks (*Rhipicephalus sanguineus*) on Dogs.

Guideline: OPPTS 810.3300

Materials and Methods: Cyphenothrin was added to Frontline plus at the rate of approximately 5% (4.76% cyphenothrin) for efficacy evaluations. Dose volumes applied were based on the Frontline label, but dilution was not taken into account for the existing fipronil, therefore fipronil dosage was slightly lower than that of Frontline alone. 18 dogs were allocated to 3 groups of 6 dogs each. Group 1, untreated control; Group 2, Frontline+cyphenothrin, Groups 3, Frontline alone.. Dogs were infested with 100 fleas and 50 ticks one day before treatment, and again at 7, 14, 21, 28, and 35 days after treatment. Counts were made at 1 and 4 hours post treatment and also after every reinfestation—this was to measure speed of kill and/or repellency. Counts were also made at 24 and 48 hours after initial infestation and all re-infestations. Parasites were not removed until the final count. Mortality was calculated using Abbott's formula. For speed of kill/repellence, the number of killed/repelled fleas on the liner below each treated dog was divided by the total number of fleas placed on the dog (all x 100), adjusted for 'normal' attrition on control dogs.

Study Summary of the Results:

1. Mean efficacy against fleas and ticks exceeded 90% when assessed at 1-2 days after treatment or reinfestation with parasites, through 35 days after treatment.
2. Immediate efficacy on fleas (i.e. kill/repellence within 4 hours of treatment) ranged from 0-75% for 1-4 hours immediately after treatment. With reinfestations after 7, 14, 21, 28, and 35 days from treatment, efficacy exceeded 90% within 4 hours for all only the 7 day reinfestation. Efficacy did not exceed 90% within 4 hours for reinfestations on days 14, 21, 28, or 35 days after treatment.
3. Immediate efficacy on ticks ranged from 11-71% for 1-4 hours immediately after treatment. With reinfestations after 7, 14, 21, and 28 days from treatment, efficacy exceeded 90% within 4 hours for only the 7 day reinfestation. Efficacy did not exceed 90% within 4 hours for reinfestations on days 14, 21, 28, or 35 days after treatment.

Entomologist's Observations/Dicussion:

1. Efficacy against fleas and ticks was adequate to support controls claims through 35 days (one month) after treatment.
2. While immediate efficacy against fleas and ticks was marginally enhanced when assessed at 1 and 4 hours after treatment (or reinfestation) compared to fipronil alone,

the immediate efficacy did not exceed 90% with any consistency for the treatments evaluated immediately 1-4 hours after initial treatment or reinfestation beyond 7 days after treatment. This data does not support any claims for faster kill or repellence due to the addition of cyphenothrin.

MRID 48129813

Title: Comparative efficacy evaluation of Sergeant's Squeeze-on and Frontline Plus for the treatment of adult cat flea (*Ctenocephalides felis*) and tick (*Haemaphysalis elliptica*, *Rhipicephalus sanguineus*, and *Dermacentor variabilis*) infestations on dogs.

Guideline: OPPTS 810.3300

Materials and Methods: Cyphenothrin was added to Seargeant's Fipronil-Methoprene formulation Frontline plus at the rate of approximately 5% for efficacy evaluations. This treatment was compared to fipronil-methoprene alone, and a positive control, Merial's Frontline Plus. Dose volumes applied were based on a titration by which dogs received 0.067 mL/kg body weight, to simulate the dosing at the high end of each respective weight class. Dogs were subgrouped by weight class with 6 dogs in each subclass (split over time to 3 dogs of each class in 2 consecutive studies). Group 1, untreated control; Group 2, Fipronil+Methoprene, Group 3, Fipronil+Methoprene+cyphenothrin, Group 4, Frontline Plus. Dogs were infested with 100 fleas and 50 ticks one day before treatment, and again at 7, 14, 21, and 28 days after treatment. Counts were made at 1 and 4 hours post treatment and also after every reinfestation—this was to measure speed of kill and/or repellency. Counts were also made at 24 and 48 hours after initial infestation and all re-infestations. Parasites were not removed until the final count. Mortality was calculated using Abbott's formula. For speed of kill/repellence, the number of killed/repelled fleas on the liner below each treated dog was divided by the total number of fleas placed on the dog (all x 100), adjusted for 'normal' attrition on control dogs.

Study Summary of the Results:

1. Mean efficacy against fleas exceeded 90% when assessed at 2 days after treatment or reinfestation with parasites, through 28 days after treatment.
2. Immediate group mean efficacy on ticks (all species) overall means were all below 90%.

Entomologist's Observations/Dicussion:

1. Efficacy against fleas and ticks was adequate to support controls general claims through 35 days (one month) after treatment.
2. No immediate efficacy claims (i.e., within 1-4 hours of application or reinfestation by parasites) are supported by this data.

Overall Review of Label Claims and Directions:

Based upon submitted efficacy data, claims are supported for fleas and ticks through 35 days. Claims for immediate efficacy are not supported except to state “starts killing within hours” or “starts killing in as little as one hour”. No data was cited or submitted in this application to support any claims against mosquitoes, therefore, any such claims must be deleted from the label. Repellence claims for fleas and ticks are not supported and must be removed from the label

Line by Line Review of Label Claims

[[Kills mosquitoes][within 24 hours for the first 7 days of treatment, and within 48 hours for up to 28 days]: Unacceptable

Kills mosquitoes that may transmit heartworm: Unacceptable

[Kills [and repels] adult fleas (in as little as 1 hour)]: Unacceptable unless modified to ‘starts killing’ adult fleas. Repels claim must be deleted.

Kills newly emerged fleas (in as little as 1 hour) before they lay eggs]: Unacceptable unless modified to ‘starts killing’

Kills [and repels] fleas, source of flea allergy dermatitis [, flea bite anemia] and tapeworm infestations: Acceptable, except that the repels claim must be deleted.

Kills [and repels] fleas {in as little as 1 hour): Unacceptable unless modified to ‘starts killing’. Also, the repels claim must be deleted.

Kills [&] [and] Repels fleas (in as little as 1 hour): Unacceptable unless modified to ‘starts killing’. Also, the repels claim must be deleted.

Kills [&] [and] Repels fleas (in as little as 1 hour) Up to [4 weeks] [1 month] [30 days]!: Unacceptable unless modified to ‘starts killing’. Also, the repels claim must be deleted. Control is supported for the durations listed.

If dog is at high risk of flea reinfestation a once monthly application may be needed: Acceptable

Kills [chewing] lice and aids in control of sarcoptic mange: Acceptable

Flea [&] [and] Tick Control for Dogs [&] [and] Puppies 12 weeks old and older: Acceptable

Kills Fleas (in as little as 1 hour), Ticks (in as little as 1 hour), [and] chewing lice [&] [and] mosquitoes: Unacceptable unless modified to ‘starts killing’. Also, the mosquitoes claim must be deleted.

Kills [&] [and] [repels] Fleas (in as little as 1 hour), Ticks (in as little as 1 hour), [and kills chewing lice] [and] [mosquitoes]: Unacceptable unless modified to 'starts killing'. Also, the repels claim must be deleted.

Monthly flea, tick, mosquito, and lice treatment: Acceptable, except Mosquito claim must be deleted.

[Four] [4] way protection . . .: Unacceptable nebulous claim.

[4 Week] [1 month] [30 day] Flea and Tick Treatment, [Flea, Tick Mosquito and Lice Treatment]: Acceptable, except Mosquito claim must be deleted.

Kills [&] [and] Repels Fleas (in as little as 1 hour) and Ticks (in as little as 1 hour) for up to [4 weeks] [1 month] [30 days]!: Unacceptable unless modified to 'starts killing'. Also, the repels claim must be deleted.

Once A Month Flea and Tick Treatment: Acceptable

Use [brand name] monthly to control Ticks (in as little as 1 hour) and chewing lice: Unacceptable unless modified to 'start killing'.

Monthly flea, tick, mosquito, and chewing lice protection: Acceptable, except Mosquito claim must be deleted.

Starts killing fleas and ticks in as little as 1 hour [and continues to kill for a month]: Acceptable

Flea & Tick Control for Dogs & Puppies 12 weeks old and older: Acceptable

Kills [and repels] Fleas (in as little as 1 hour), Ticks (in as little as 1 hour), and kills chewing lice & mosquitoes: Unacceptable unless modified to 'starts killing'. Also, the repels claim must be deleted, and the mosquitoes claim must also be deleted.

Kills [and] [&] [repels] Ticks (in as little as 1 hour) including those that may transmit Lyme disease: Unacceptable unless modified to 'starts killing'. Also, the repels claim must be deleted.

Kills [and] [&] [repels] Ticks (in as little as 1 hour) for Up to [4 weeks] [1 month] [30 days]!: Unacceptable unless modified to 'starts killing'. Also, the repels claim must be deleted.

Kills Deer Ticks [that] [transmit Lyme Disease,] for up to [4 weeks] [1 month] [30 days]: Acceptable

Kills [and] [&] [repels] Ticks (in as little as 1 hour), Kills Deer Ticks for up to [4 weeks] [1 month] [30 days]!: Unacceptable unless modified to 'starts killing'. Also, the repels claim must be deleted.

Kills [Brown Dog Ticks], [American Dog Ticks,] [and Lone Star Ticks] [(*Rhipicephalus sanguineus*)] (in as little as 1 hour) for up to [4 weeks] [1 month] [30 days]: Unacceptable unless modified to ‘starts killing’.

Kills [and] [&] [repels] [Brown Dog Ticks], [(*Rhipicephalus sanguineus*)] (in as little as 1 hour) for up to [4 weeks] [1 month] [30 days]: Unacceptable unless modified to ‘starts killing’. Also, the repels claim must be deleted.

Kills American Dog Ticks [and] [(*Dermacentor variabilis*)] for up to [4 weeks] [1 month] [30 days]!: Acceptable

Dogs can be bathed 24 hours after treatment: Unacceptable.

Long lasting: Acceptable.

Prevents reinfestation: Unacceptable unless qualified by pest and a duration—i.e., ‘prevents reinfestation of listed pests for 30 days’.

Fast Action against chewing lice infestations: Unacceptable, as no data was submitted or cited regarding speed of kill for lice.

Aids in Control of Sarcoptic Mange [infestations]: Acceptable.

BACK/SIDE CARTON LABEL-MASTER LABEL

[brand name] contains Fipronil, cyphenothrin to effectively kill [and repel] Fleas [(in as little as 1 hour)], Ticks [(in as little as 1 hour)], and kills mosquitoes and (chewing) lice. The active ingredients in [brand name] work by collecting in the hair follicles and skin oils. This product features a sustained-release formula that discharges from the animal’s hair follicles using the natural skin oils, resulting in fast acting [and long lasting] control of Fleas and Ticks [(in as little as one hour)], [and kills mosquitoes] and chewing lice [for 30 days]: All repels claims must be removed from the label. All references to action in as little as 1 hour must be revised to ‘starts acting’ or ‘starts killing’ or alternatively, the claims of ‘in little as 1 hour’ can be removed. ‘Fast acting’ claim must be removed. Mosquito claim must be removed. The claims about movement in hair follicles is deferred to the RM Reviewer and PM.