

EFFICACY REVIEW

PRODUCT: ProMeris for Dogs
DATE: December 2, 2008
REG NUMBER: 80490-2
DB BARCODE: D 357599
DECISION: 400894
GLP: Varied
CHEMICAL: Metaflumazone (14.34%)
Amitraz (14.34%)
CHEMICAL NUMBER: Metaflumazone - 281250
Amitraz - 106201

PURPOSE: Review data to determine if it supports claims for (1) that the kill of ticks is a rapid event occurring within 24 hours for most tick species and (2) that that the product can be administered at the base of a dog's skull as an alternative applications site

MRIDS:

47569301. *Efficacy of a Single Dose of a Topically Applied Spot-on Formulation of Metaflumaizone combined with Amitraz to Repel, Prevent Attachment and Kill Amblyomma americanum and Dermacentor variabilis*

47569302. *Efficacy of a Topically Applied Spot-on Formulation of Metaflumizone Combined with Amitraz to Detach, Repel, Inhibit Feeding, and Kill Brown dog Ticks on Dogs*

47569303. *Efficacy of a Single Dose of Topically Applied Spot-on Formulation of Metaflumizone combined with Amitraz to Repel, Prevent Attachment and Kill Rhipicephalus sanguineus*

47569304. *Compared Efficacy of a Single Dose of Topically Applied Spot-on Products to Repel, Prevent Attachment and Kill Ixodes Scapulars*

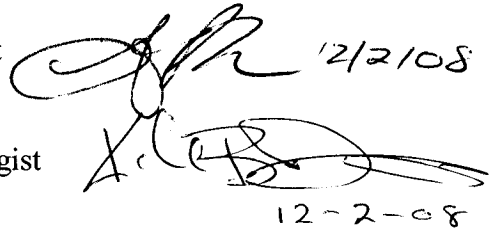
47569305. *Comparative Efficacy Study of ProMeris on Controlling Flea (Ctenocephalides felis) and Tick (Rhipicephalus sanguineus) Infestations on Dogs after a Single Dose is Applied Between the Shoulder Blades or Behind the Skull*

47557806

~~**47569306.** *Efficacy of a Topically Applied Spot-on Formulation of Metaflumizone Combined with Amitraz to Repel, Prevent Attachment and Kill American Dog Ticks (Dermacentor variabilis)*~~

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12/2/08
12-2-08

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BACKGROUND

ProMeris for dogs is a topical spot-on insecticide treatment for the control of fleas, ticks, chewing lice and Demodectic mange mites for dogs and puppies 8 weeks of age and older. The product is applied on the skin between the shoulder blades once monthly.

Labeled Application Rates:

Dog Size	Application Rate
Dogs 11lbs and under	.023 fl oz
Dogs 11-22 lbs	.045 fl oz
Dogs 22-55 lbs	.113 fl oz
Dogs 55-88 lbs	.180 fl os
Dogs 88-110 lbs	.225 fl os

DATA REVIEW

The following data review is comprised of explanations of materials and methods, and a summation of experimental results containing tables with reformatted data.

MRID 47569301 - Efficacy of a Single Dose of a Topically Applied Spot-on Formulation of Metaflumaizone combined with Amitraz to Repel, Prevent Attachment and Kill Amblyomma americanum and Dermacentor variabilis

The objective of this study was to evaluate efficacy of commercial doses of metaflumizone + amitraz compared with positive and non-treated controls against weekly (tick) challenges on beagle dogs > 6 months old. 12 male and 12 female dogs were used and groups were divided randomly with excel between weight classes.

Dogs were divided into 4 groups of 6 dogs each and dosed as directed by each product. European commercial product for ProMeris was given which contains 15% metaflumazone and 15% amitraz (the American product contains 14.34% of each.) Positive controls given were Frontline Plus which contains Fipronil plus (s) methoprene and K9 Advantix which contains Imidacloprid plus permethrin. All dogs were dosed on day 0 and infested with 50 of each species of un-fed ticks on days 7, 14, 21, & 28 in stainless tubs. For the next 10 minutes, staffers re-applied any ticks that fell off. After the 10 minute time period, dogs were returned to their runs and any ticks that had fallen off were examined at 4 and 24 hours for viability. At hours 4, 24 & 48 dogs were examined and live attached ticks were recorded.

RESULTS:

TABLE 1. Geometric mean of live attached *Amblyomma americanum* (Lone star tick) counts and percent efficacy

Geometric Mean & % Efficacy on Day/Hour after Infestation				
Treatment	7/24	14/24	21/24	28/24
non-treated	17	16.3	18.9	13.7
Metaflumazone + Amitraz	5.9 65.4%	0.6 96.6%	4.0 78.9%	4.2 69%

TABLE 2. Geometric mean of live attached *Dermacentor variabilis* (American dog tick) counts and percent efficacy

Geometric Mean & % Efficacy on Day/Hour after Infestation				
Treatment	7/24	14/24	21/24	28/24
non-treated	23.4	22.6	20.3	10.4
Metaflumazone + Amitraz	0.5 97.8%	0 100%	2.9 85.6%	2 80.9%

Based on the data for the mean live attached ticks, within 24 hours the efficacy for Metaflumazone + Amitraz was $\geq 80.9\%$ up to day 29 for the *D. variabilis* species and $\geq 65.4\%$ for the *A. americanum* tick. At 24 and 48 hours, all treatments resulted in significantly lower geometric means for live attached ticks of both species relative to non-treated controls ($P < .05$). At 4 hours, only the Imidacloprid plus permethrin treatment showed a significant reduction in ticks ($P < .05$), which occurred on days 7 and 14 for *A. americanum* ticks and on day 14 and 21 for the *D. variabilis* ticks. Both imidacloprid plus permethrin and metaflumazone + amitraz showed significant reductions in ticks at 4 hours for the *D. variabilis* ticks on day 7.

The first tick infestation challenge was on day 7. Since treatment was on day zero, it is not possible to assess a “24 hour rapid” claim, since the first “24 hour” time period was 8 days after treatment.

TABLE 3. Arithmetic mean numbers of *Amblyomma americanum* ticks collected from the tub after each infestation and percent mortality of ticks at 4 and 24 hours after collection

Treatment	DAY7			DAY 14			DAY21			DAY 28		
	Tub mean	% Mortality		Tub mean	% Mortality		Tub mean	% Mortality		Tub mean	% Mortality	
		4 hr	24 hr		4 hr	24 hr		4 hr	24 hr		4 hr	24 hr
non-treated	23.8	2.8	6.3	14.0	3.6	3.6	20.3	2.0	5.8	20.8	17.0	28.0
Metaflumazone + Amitraz	22.2	6.7	40.4	17.8	6.4	16.9	20.5	2.5	13.0	14.7	11.7	19.3

TABLE 4. Arithmetic mean numbers of *Dermacentor variabilis* ticks collected from the tub after each infestation and percent mortality of ticks at 4 and 24 hours after collection

Treatment	DAY7			DAY 14			DAY21			DAY 28		
	Tub mean	% Mortality		Tub mean	% Mortality		Tub mean	% Mortality		Tub mean	% Mortality	
		4 hr	24 hr		4 hr	24 hr		4 hr	24 hr		4 hr	24 hr
non-treated	1.7	0.0	0.0	1.5	0.0	0.0	0.5	25.0	25.0	2.0	20.0	28.0
Metaflumazone + Amitraz	3.0	0.0	0.0	2.5	5.6	5.6	0.8	37.5	37.5	6.8	20.6	0.0

Based on the data tables, the percent efficacy of mortality for both species of ticks was very low for the Metaflumazone + Amitraz product. The highest rate for this product was 40.4% on day 7 at 24 hours for the *A. americanum* ticks. For the *D. variabilis* ticks, for days 7 and 28 at 24 hours the Mortality was at 0% (the control at day 28 was 28% at 24 hours). On day 21 at 24 hours was the highest percent mortality for this species at 37.5%.

MRID: 47569302 - Efficacy of a Topically Applied Spot-on Formulation of Metaflumizone Combined with Amitraz to Detach, Repel, Inhibit Feeding, and Kill Brown dog Ticks on Dogs

The objective of this study was to evaluate efficacy of a commercial spot-on formulation of metaflumizone and amitraz against brown dog ticks (*R. sanguineus*) on dogs as compared with a non-treated control and two positive controls.

For this study, 4 groups of 8 adult beagles were used ranging in ages of 5-8 years. 19 male and 13 female dogs were used and groups were divided randomly with excel between weight classes. European commercial product for ProMeris was given which contains 15% metaflumazone and 15% amitraz (the American product contains 14.34% of each.) The positive controls given were Fipronil plus (s) methoprene and Imidacloprid plus permethrin. Treatment was given on day 0 and dogs were infested with 50 adult brown dog ticks on days, -2, 5, 12, 19, 26, 33, 40 & 47. Before infestations, ticks were weighed in batches and the weight was divided by the number of ticks to obtain a mean pre-infestation weight.

At hours 2 & 24 after infestations, the number of live attached, live un-attached and dead ticks was recorded (then all ticks were removed). Up to 10 randomly selected ticks from each dog during collection after each infestation were weighed and dissected to determine post-infection weight and the presence of blood to determine if it had fed while on the dog.

RESULTS:

Geometric Mean & % Efficacy on Day/Hour after Infestation

Treatment	0/24	5/24	12/24	19/24	26/24	33/24	40/24	47/24
non-treated	19.3	17.8	12.4	17.8	19.8	20.9	19.6	20.8
Metaflumazone + Amitraz	5.3 72.5%	0.5 99.5%	0 100%	20.4 100%	0 100%	0 99.1%	29.3 94.1%	2.9 68.8%

None of the treatments showed significant declines of mean live attached ticks on the already infested dogs by the 8-hour mark. Within 24 hours however, counts for all 3 treatments were

significantly lower than the control with efficacies $\geq 57.1\%$ ($P < .05$). By 48 hours, all three treatment groups were $\geq 84.8\%$ efficacious. Metaflumizone plus amitraz attained 72.5% efficacy within 24 hours and 92.8% within 48 hours of the treatment on already infested dogs.

From days 5-28 at 2, 24 and 48 hours after each infestation, each treatment group had $\geq 98.7\%$ efficacy and many even had 100% efficacy at most time periods for live attached ticks. At day 33, each treatment group showed a slight decline in efficacy but each maintained $\geq 92.80\%$ efficacy by 48 hours up to day 42. Therefore, except at day 1, which had a 72.5% efficacy rate at 24 hours, ProMeris provided $\geq 92.8\%$ efficacy up to day 40 within 24 hours of each infestation.

Of the few live ticks that were collected from dogs, most had fed. Very few unfed ticks were recovered from any animal and there were no significant differences ($P < .05$) observed between treated and control dogs. Weights of ticks collected from dogs followed a similar pattern, in that when live ticks were recovered, their weights showed no marked difference between treated and non-treated dogs. On day 2, an average 2.1 ticks were found on the dogs and all were fed. No other ticks were found until day 35 (since they only pulled the ticks off at the 48 hour mark), which had also fed.

MRID: 47569303 - Efficacy of a Single Dose of Topically Applied Spot-on Formulation of Metaflumizone combined with Amitraz to Repel, Prevent Attachment and Kill *Rhipicephalus sanguineus*

The objective of this study was to evaluate efficacy of a commercial spot-on formulation of metaflumizone and amitraz against brown dog ticks (*R. sanguineus*) on dogs versus non-treated control and two positive controls against weekly (tick) challenges. In the study, 12 male and 12 female beagle dogs >6 months were used and were divided into four groups of 6 dogs each. European commercial product for ProMeris was given which contains 15% metaflumazone and 15% amitraz (the American product contains 14.34% of each.) The positive controls were Fipronil plus (s) methoprene and Imidacloprid plus permethrin. Dogs were treated on day 0 and infested with ticks on days 7, 14, 21 & 28 with 50 unfed brown dog ticks. For the next 10 minutes, staffers re-applied any ticks that fell off. After the 10 minute time period, dogs were returned to their runs and any ticks that had fallen off were examined at 4 and 24 hours for viability. At hours 4, 24 & 48 dogs were examined and live attached ticks were recorded.

RESULTS

Geometric Mean & % Efficacy on Day/Hour after Infestation				
Treatment	7/24	14/24	21/24	28/24
non-treated	16.5	22	22.1	19.2
Metaflumazone + Amitraz	.1 99.3%	0.5 97.7%	.8 96.3%	4.8 74.8%

The geometric mean showed that metaflumizone attained >74.8% efficacy for the live attached ticks at every 24 hour period after infestations. 74.8% was achieved on day 29 and 96.3% was the next lowest, achieved on day 22. The other positive controls showed similar results except

for fipronil + (s) methoprene on day 22 at only 74.9% and on day 29 at 45.2%. All treatments resulted in significantly lower geometric means of live attached ticks when compared with non-treated controls ($P < .05$) at 4, 24, and 48 hours on days 7 & 14, except for fipronil + (s) methoprene at 4 hours on day 14. All three treatments provided effective tick control through 4 weeks of treatment, providing $>97.2\%$ control within 48 hours of infestations up to day 21 and $\geq 81.9\%$ control within 48 hours after day 28. Metaflumizone plus amitraz showed significantly lower geometric means of live attached *R. sanguineus* counts against non-treated controls ($P < .05$) within 24 hours after each infestation. Efficacy was $\geq 96.3\%$ for Metaflumizone plus amitraz within 24 hour up to day 22 and was at 74.8% on day 29. The first challenge of infesting the dogs with ticks was 7 days after treatment, therefore it is not possible to assess a “24 hour rapid” claim, since the first “24 hour” time period was 8 days after treatment.

Arithmetic controls showed similar results except for on day 30 at 48 hours after infestation. The mean live attached tick count was 9.7, however no efficacy calculations were done for arithmetic means.

Treatment	DAY7			DAY 14			DAY21			DAY 28		
	Tub mean	% Mortality		Tub mean	% Mortality		Tub mean	% Mortality		Tub mean	% Mortality	
		4 hr	24 hr		4 hr	24 hr		4 hr	24 hr		4 hr	24 hr
non-treated	3.2	Not Done	16.7	.7	0	0	4.2	0	0	4.7	2	4
Metaflumazone + Amitraz	1.7	Not Done	60	1.8	0	0	4.5	25	0	2.2	0	0

Metaflumizone plus amitraz showed little to no mortality on the collected *R. sanguineus* ticks that had fallen off the dogs after the 10-minute period of infesting them. On day 7, there was a 60% mortality (mean of 1.7 ticks). Every other day showed 0% mortality, which was similar to or less than the non-treated control. Fipronil + (s) methoprene showed 100% mortality on day 7 (mean 1.5 ticks), 20% on day 14, 0% on day 21 and 30% on day 28. Only imidacloprid showed high mortality rates (80.6-100%), but it was not indicated if this was statistically significant.

MRID: 47569304 - Compared Efficacy of a Single Dose of Topically Applied Spot-on Products to Repel, Prevent Attachment and Kill *Ixodes Scapularis*

The objective of this study was to evaluate efficacy of commercial doses of ProMeris, K9 Advantix and Frontline Plus against *I. scapularis* (black legged) ticks on dogs compared with a non-treated control. In the study, 12 male and 12 female beagle dogs >6 months were used and were divided into four groups of 6 dogs each. European commercial product for ProMeris was given which contains 15% metaflumazone and 15% amitraz (the American product contains 14.34% of each.) The positive controls were Frontline Plus (Fipronil plus (s) methoprene) and K9 Advantix (Imidacloprid plus permethrin). Dogs were treated on day 0 and infested with ticks on days 7, 14, 21 & 28 with 50 black legged ticks. For the next 10 minutes, staffers re-applied any ticks that fell off. After the 10 minute time period, dogs were returned to their runs. At hours 4, 12, 24 & 48 after each infestation, dogs were examined and live attached ticks were recorded.

RESULTS

Geometric Mean & % Efficacy on Day/Hour after Infestation				
Treatment	7/24	14/24	21/24	28/24
non-treated	12.4	10.77	14.59	11.1
Metaflumazone + Amitraz	.35 97.1%	0.62 94.3%	1.82 87.5%	5.2 53.1%

The geometric means for dogs treated with ProMeris showed a significant decrease in ticks than those in the non-treated control group, except on day 28 at 4 and 12 hours ($P < .05$). Dogs treated with ProMeris had $\geq 87.5\%$ efficacy within 24 hours of infestation on days 7, 14 & 21. At day 28, the efficacy decreased to 53.1% at 24 hours (but reached 81.1% by 48 hours). Both Frontline Plus and K9 Advantix showed a significant decrease in *I. scapularis* ticks over the non-treated group at every count ($P < .05$). The first challenge of infesting the dogs with ticks was 7 days after treatment, therefore it is not possible to assess a “24 hour rapid” claim, since the first “24 hour” time period was 8 days after treatment.

In addition, this study only looked at “live attached” ticks and did not compare or record data for “killed” ticks.

MRID: 47569305 – Comparative Efficacy Study of ProMeris on Controlling Flea (*Ctenocephalides felis*) and Tick (*Rhipicephalus sanguineus*) Infestations on Dogs after a Single Dose is Applied Between the Shoulder Blades or Behind the Skull

The objective of this study is to determine if applying ProMeris behind the skull is equally effective as when applied behind the shoulder blades of dogs. In the study, 13 male and 11 female young adult (≥ 6 months old) beagle dogs were used. The dogs were individually housed in indoor pens and were broken up into 3 groups of 8: A) non-treated control, B) ProMeris given at the base of skull & C) ProMeris given between shoulder blades.

Commercial dosing of pre-packaged supplies of ProMeris was given at rates of 1.33ml for dogs 5-9.9kg or 3.33ml for dogs 10-24.9kg. The schedule of the study was as follows:

Day -1	All dogs Infested with 100 adult unfed fleas and 50 ticks
Day 0	Dogs were dosed accordingly
Day 2	(48 hours after treatment) Each dog examined and all fleas & ticks were collected with live ones recorded in number
Days: 5, 12, 19, 26, 33, 40	Dogs were re-infested same as above
Days: 7, 14, 21, 27, 35, 42	(48 hours after treatment) dogs examined and all fleas & ticks were collected with live ones recorded in number

RESULTS:

FLEA

Geometric Mean & Efficacy of Flea counts based on day

	2	7	14	21	28	35	42
non-treated	69.07	67.99	49.48	55.19	65.13	71.58	72.16
behind skull	.15 99.8%	.09 99.9%	0 100%	0 100%	0 100%	.45 99.4%	8.96 87.6%
between shoulder blades	.15 99.8%	0 100%	0 100%	0 100%	0 100%	.36 99.5%	.62 99.1%

Flea counts based on geometric means for groups B, Promeris given behind base of skull and C Promeris given between shoulder blades, were not statistically different from one another and were $\geq 98.8\%$ efficacious up to day 35. On day 42, dogs with treatment between shoulder blades had higher efficacy at 99.1 % vs. 87.6% at the base of skull.

TICKS

Geometric Mean & Efficacy of Tick counts based on day

	2	7	14	21	28	35	42
non-treated	34.77	34.44	30.34	29.79	30	29.93	30.6
behind skull	.19 99.5%	.19 99.5%	.09 99.7%	1.75 94.1%	11.53 61.6%	18.02 39.8%	23.21 24.1%
between shoulder blades	1.07 96.9%	.09 99.7%	.09 99.7%	.93 96.9%	10.82 63.9%	16.46 45%	19.75 35.5%

There was no statistical difference between groups B, Promeris given behind base of skull and C Promeris given between shoulder blades, up to day 35. For the group given treatment at the base of skull, efficacy was $\geq 94.1\%$ at all time periods up to day 21. At day 28, efficacy for both groups dropped below 90% and was at 61.6% behind skull vs. 63.9% between the shoulder blades.

47557806

47569306. Efficacy of a Topically Applied Spot-on Formulation of Metaflumizone Combined with Amitraz to Repel, Prevent Attachment and Kill American Dog Ticks (*Dermacentor variabilis*)

The objective of this study was to evaluate efficacy of commercial dosing of ProMeris on American Dog ticks (*D. variabilis*) on dogs compared with a non-treated control and two positive controls, Frontline Plus and K9 Advantix against an existing infestation and weekly post-treatment challenges.

15 male and 17 female dogs were used and groups were divided randomly with excel between weight classes. European commercial product for ProMeris was given which contains 15% metaflumazone and 15% amitraz (the American product contains 14.34% of each.) The positive

controls were Frontline Top Spot (fipronil) and K9Advantix (imidacloprid plus permethrin). Dogs were treated on day 0 and on days -5, 7, 14, 21, 28, 35, 42 49 & 55 fifty unfed ticks were placed in the center of a carpet piece with dogs in an infestation chamber for 3-5 hours. At hours 4, 12, 24 & 48 dogs were examined and live attached and live unattached ticks were recorded (only attached tick data was analyzed). On day 55 however, dogs were infested but ticks were not counted until 48 hours later and the Advantix group was withdrawn due to a drop in efficacy below 60%.

RESULTS

**Geometric Mean & % Efficacy
on Day/Hour after Infestation**

Treatment	0/24	7/24	14/24	21/24	28/24	35/24	42/24	49/24
non-treated	21.22	25.73	22.4	23.31	24.18	22.34	23.87	20.24
Metaflumazone + Amitraz	1.61 92.42%	0 100%	0 100%	.82 96.5%	0 100%	.22 99%	5.96 75.02%	2.29 88.68%

On day 0, within 24 hours of the treatment, efficacy was up to 92.42% against a current infestation of ticks. At every 24 and 48 hour mark post-infestation, ProMeris provided significantly high efficacy ($P < .05$) against *D. variabilis* ticks with $\geq 92.4\%$ within 24 hours up to day 37 and $\geq 75.02\%$ up to day 51, which was equal to or higher than the positive controls Frontline Top Spot or Advantix.

Based on the efficacy analysis for geometric means, ProMeris never showed a 90% efficacy rate at the four hour mark post infestations to provide evidence for “repelling” *D. variabilis* ticks, however it did show a drastic decrease in ticks at 4 hours as compared with the non-treated control group. Efficacy was $\geq 60.77\%$ at 4 hours with ProMeris up to day 35 with its highest rate at 84.44% on day 14, which was equally effective to at least one of the positive control treatments throughout the study.

RECOMMENDATIONS:

Claim 1 – Kill of ticks is a rapid event occurring within 24 hours

The submitted data partially support this claim. Out of the 5 studies submitted for this claim, only two challenged the product with ticks within 24 hours of application; therefore only these two studies could be reviewed for this claim. Of these two studies, only one achieved $>90\%$ efficacy within 24 hours of application.

Not every weight class was tested and none of the studies proved that the ticks were killed, only that there was a significant percent decrease in number of ticks attached to the dogs. In addition, the European brand of ProMeris was used in every study, which has a higher percent of active ingredient. The American product will likely not have as high of efficacy as this product.

Recommended label adjustments:

Remove claims, “Rapidly kills ticks” and “kills and controls most tick species within 24 hours.”

Alternatively, the above claims can be revised to read “Starts killing most tick species within 24 hours.”

To have the proposed claims added to the label, additional data must be submitted that show high efficacies within 24 hours of application on each weight class. The product as formulated and sold in the United States must be used in the studies and should show that the product causes mortality of ticks.

Claim 2 – The product can be administered at the base of dog’s skull as an alternative application site.

The submitted data support this claim and directions implicating application at either site is acceptable.