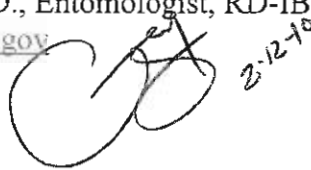


Efficacy Review

Date: February 12, 2010

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Products: Etofenprox/Nylar Spot-on Flea and Tick for Dogs

EPA Reg. #: 2517-RGG

A.I.'s: Ethofenprox (55.0%), Pyriproxyfen (2.2%)

Decision #s: 420097

DP #s: 371691

Submission: R310, New Products, RD Science Review

MRIDs: Submitted: 47849601, 47849602, 47849603, 47849604, 47849605,
47849606

GLP: No

MRID 47849601:

Title: Efficacy of a Water-Based Etofenprox Spot-on against Fleas and Ticks on Small Dogs

Guideline: OPPTS 810.3300

Materials and Methods: 2 experimental groups of dogs, 6 dogs in each group, with weights ranging from 4.5-12.2 lbs. One group was a treatment group and one was a control. Treated dogs were dosed with 1.5 mL of a 55% etofenprox spot-on. Infestations (and reinfestations over time) were conducted with 50 ticks (*R. sanguineus*) and 100 cat fleas (*C. felis*). Fleas were counted at both 24 hours and 72 hours after each infestation/reinfestation. Ticks were counted by hand. Removal of both was done at 72 hours for mortality assessments. Weekly reinfestations were conducted until inadequate efficacy was shown. % Mortality was calculated in comparison to the control.

Study Summary of the Results:

1. Due to varying dog weights, the effective dose applied ranged between 150-407 mg/kg (mean of 231 mg/kg). Dogs ranged in weight from 4.5-12.2 lbs.
2. Efficacy against fleas was only adequate through 16 days.
3. Efficacy against ticks was adequate through 31 days (mean efficacy of 94%).
4. The dose applied is less than proposed on the label (2.0 mL for dogs 4-20 lbs).

Entomologist's Observations/Discussion:

1. While the data support efficacy claims on dogs for ticks through 30 days, the study is limited by the lack of dogs at the upper margin of the weight class, which would be the most likely to have an inadequate level of coverage by a 2.0 mL application.
2. Because the rate applied is less than what is proposed on the product label, an approximation can be made based on the titration. For example, if 1.5 mL is adequate for a 12 pound dog, then 2.0 mL would only be adequate for dogs up to 16 lbs (for ticks only).
3. Flea efficacy was not adequately supported by this study.

MRID 47849602:

Title: Efficacy, at Minimum Dose Rate, of an Etofenprox Spot-on against Fleas and Ticks on Small Dogs

Guideline: OPPTS 810.3300

Materials and Methods: 17 dogs were allocated to 3 treatment groups (5-6 dogs each). One was an untreated control group, and the other groups were both treated with an etofenprox squeeze on, applied at 2 different dosages (2 mL and 4 mL, respectively). Dogs were grouped by size so that all dogs received an approximate dosage of 250 mg/kg of etofenprox, as a minimum. Group B dogs were all approximately 7-10 lbs, while Group C dogs were approximately 18-20 lbs. Infestations (and reinfestations over time) were conducted with 50 ticks (*R. sanguineus*) and 100 cat fleas (*C. felis*). Fleas were counted via a comb at both 24 hours and 72 hours after each infestation/reinfestation. Ticks were counted by hand. Removal of both was done at 72 hours for mortality assessments. Weekly reinfestations were conducted until inadequate efficacy was shown. % Mortality was calculated in comparison to the control.

Study Summary of the Results:

5. For Group B dogs receiving 2.0 mL of treatment, flea and tick efficacy is adequate through 22 days after treatment. For Group C dogs receiving 4.0 mL of treatment, efficacy is adequate through 29 days after treatment.

Entomologist's Observations/Discussion:

1. While the study was designed to assess a 'minimum' dosage (250 mg etofenprox/kg animal), this meant that animals at the upper range of the the weight classification (i.e.,

20 lb dogs) received a treatment that is approximately double the dose instructed on the product label (2 mL product for dogs weighing 4-20 lbs).

2. Therefore, dogs in group C were treated with more material than what is on the proposed product label. The data from this study would only support efficacy claims for dogs under 10 lbs, which received 2 mL per animal, and those claims would only be valid for 22 days after treatment, not a full 30 days.

MRID 47849603:

Title: Efficacy, at Label Dose Volume and at Minimum Dose Rate, of an Etofenprox Spot-on against Fleas and Ticks on Small Dogs

Guideline: OPPTS 810.3300

Materials and Methods: 18 dogs were allocated to 3 treatment groups (6 dogs each). One was an untreated control group, and the other groups were both treated with an etofenprox squeeze on, applied at 2 different dosages (2.5 mL and ~4.5 mL, respectively). Dogs were grouped by size. Group B dogs were all approximately 8-9 lbs, while Group C dogs were approximately 18-20 lbs. Group B dogs were treated with 2.5 mL of spot-on per animal. Group C dogs were dosed by weight, so that each dog received 247 mg ai/kg, with applications thus varying from 4.3 mL to 4.7 mL per animal. Infestations (and reinfestations over time) were conducted with 50 ticks (*R. sanguineus*) and 100 cat fleas (*C. felis*). Fleas were counted via a comb at both 24 hours and 72 hours after each infestation/reinfestation. Ticks were counted by hand. Removal of both was done at 72 hours for mortality assessments. Weekly reinfestations were conducted until inadequate efficacy was shown. % Mortality was calculated in comparison to the control.

Study Summary of the Results:

6. For Group B, flea efficacy was adequate through 16 days after treatment.
7. For Group B, tick efficacy was 89% for 23 days after treatment and 85% for 30 days after treatment.
8. For Group C, flea and tick efficacy was adequate through 30 days after treatment.

Entomologist's Observations/Discussion:

1. Both treatment groups were treated with dosages exceeding that proposed on the submitted label, and thus the data are not valid to support efficacy claims for that proposed dosage.
2. For dosages applied as listed in the study, efficacy against fleas in Group B animals was only adequate through 16 days after treatment. Efficacy in Group C was maintained at 89% through 30 days after treatment.
3. For dosages applied as listed in the study, efficacy against ticks in Group B animals was demonstrated to be 89% at 23 days after treatment and 85% at 30 days after treatment. Efficacy in Group C was maintained through 30 days after treatment.

MRID 47849604:

Title: Evaluation of Sergeant's Etofenprox Squeeze-on Against Fleas, Ticks, and Mosquitoes on Dogs.

Guideline: OPPTS 810.3300

Materials and Methods: 12 dogs were allocated to 2 treatment groups (6 dogs each). One was an untreated control group, and the other group was treated with an etofenprox squeeze on, applied at 2.5 mL per animal. Dogs in the treatment group were all 10 lbs or less, while control dogs ranged in weight from 11-14.3 lbs. Infestations (and reinfestations over time) were conducted with 50 each of 3 species of ticks (*R. sanguineus*, *D. variabilis*, and *A. americana*) at various infestation intervals, and 100 cat fleas (*C. felis*). Fleas were counted via a comb at both 24 hours and 72 hours after each infestation/reinfestation. Ticks were counted by hand. Removal of both was done at 72 hours for mortality assessments. Weekly reinfestations were conducted until inadequate efficacy was shown. % Mortality was calculated in comparison to the control. In the 3rd and 4th weeks after treatment, all dogs were anesthetized and confined for 1 hour with 25 unfed *Aedes aegypti* or (separately) with 25 *Culex quinquefasciatus* mosquitoes, inside a screen cage. Landings were counted for 5 minutes. Dogs were removed after 1 hour and mosquitoes were recovered to assess survival and blood feeding status.

Study Summary of the Results:

9. Actual dosages applied to dogs ranged from 304-411 mg ai/kg.
10. Flea efficacy was adequate through 23 days after treatment.
11. Tick efficacy was adequate through 16 days after treatment.
12. Treatment was not lethal to either species of mosquitoes, but inhibited blood feeding >90% (compared to control) for 30 days for *Aedes* and 29 days for *Culex*.

Entomologist's Observations/Discussion:

1. Dogs were treated with dosages exceeding that proposed on the submitted label, and thus the data are not valid to support efficacy claims for that proposed dosage.
2. For dosages applied as listed in the study (2.5 mL), efficacy against fleas is only supported for 23 days after treatment for dogs under 10 lbs.
3. For dosages applied as listed in the study (2.5 mL), efficacy against ticks is only supported for 16 days after treatment for dogs under 10 lbs.
4. For the 2.5 mL doses, claims against mosquitoes for prevention of blood feeding are valid only for dogs less than 10 lbs., and no kills claims are supported for mosquitoes.

MRID 47849605:

Title: Efficacy of Sergeant's Etofenprox Squeeze-on against *Ixodes scapularis* Nymphs

Guideline: OPPTS 810.3300

Materials and Methods: 12 dogs were allocated to 2 treatment groups (6 dogs each). One was an untreated control group, and the other group was treated with an etofenprox squeeze on, applied at 2.5 mL per animal. Dogs in the treatment group were all 10 lbs or less, while control dogs ranged in weight from 11-14.3 lbs. 3 days after treatment, hair was clipped from each dog. Ten nymphal ticks placed in petri dishes with each hair sample and mortality was assessed at 24 h and 48 h after placement. % Mortality was calculated in comparison to the control.

Study Summary of the Results:

13. Actual dosages applied to dogs ranged from 304-411 mg ai/kg.
14. Efficacy was 100% for ticks exposed to hair taken 3 days after treatment (100% mortality was observed at both 24 h and 48 h after placement on hair).

Entomologist's Observations/Discussion:

1. Distribution of hair samples was not specified, and the randomization scheme was not defined (i.e., were multiple samples pooled for each dog, or were sub-replicates established for each dog?)
2. Because hair was clipped 3 days after treatment, claims against Deer ticks would only be valid for 3 days after treatment. This data would not support the one-month claim proposed on the label. A study that exposed ticks to hair taken 30 days after treatment would be required to demonstrate efficacy against deer ticks.

MRID 47849606:

Title: Efficacy of a 2 mL Unit Dose of Sergeant's Etofenprox Squeeze-on, Applied at Minimum Dose Rates, against Fleas and Ticks on Small Dogs

Materials and Methods: 12 dogs were allocated to 2 treatment groups (6 dogs each). One was an untreated control group, and the other group was treated with an etofenprox squeeze on (55%), applied at 2.0 mL per animal (as proposed on new product label). Dogs in the treatment group were all 18-20 lbs., while control dogs ranged in weight from 20-30 lbs. Infestations (and reinfestations over time) were conducted with 50 each of 3 species of ticks (*R. sanguineus*, *D. variabilis*, and *A. americana*) at various infestation intervals, and 100 cat fleas (*C. felis*). Fleas were counted via a comb at both 24 hours and 72 hours after each infestation/reinfestation. Ticks were counted by hand. Removal of both was done at 72 hours for mortality assessments. Weekly reinfestations were conducted until inadequate efficacy was shown. % Mortality was calculated in comparison to the control.

Study Summary of the Results:

15. Actual dosages applied to dogs ranged from 122-233 mg ai/kg (mean 127 mg/kg).

16. Flea efficacy was adequate through 16 days after treatment and 85% through 23 days after treatment.
17. Tick efficacy was adequate through 23 days after treatment and 80% through 30 days after treatment.

Entomologist's Observations/Discussion:

1. This is the only study where the dosage applied to animals exactly matches the dosage on the proposed label, and also used dogs at the upper margin of the 20 lbs. weight class.
2. Efficacy against fleas is only supported for 16 days after treatment and marginally for 23 days after treatment
3. Efficacy against ticks is only supported for 23 days after treatment.

Overall Review of Label Claims and Directions:

None of the studies were submitted under GLP standards, and protocols were vague on the exact specifications by which parasites were placed on animals (e.g., random anatomical distribution per 810.3300 guideline).

Claims against Deer Ticks, *Ixodes*, are not supported and must be removed from the label.

Claims against Mosquitoes are not supported for the application rate of 2.0 mL proposed on the current label. The dosage would have to be raised to support this claim, and the claim must only be for repellence/suppression of mosquito blood feeding. Kills and/or control claims are not supported by the data.

The preponderance of data indicates that a 2.0 mL application of the proposed 55% etofenprox product is not adequate to protect dogs on the upper end of the weight class for the 30 day retreatment interval from fleas and ticks. If animal safety data are adequate, the registrant should label the product for different application rates to different weight classes of dogs. Some variability is evident even when the dosage is raised to 2.5 mL for small dogs under 10 lbs. For dogs between 10-20 lbs, the dosage should be raised to 4.5-5.0 mL in order to support the label claims of control of fleas and ticks for 30 days.

Claims against flea eggs and larvae are not supported by this data and must be removed from the label. Also, claims regarding breakage of the flea life cycle and prevention of flea eggs from developing for up to 9 weeks (70 days) after application are not supported and also must be removed.

Removal of unacceptable claims is deferred to the RM reviewer and PM, as some claims may possibly be acceptable under conditional registrations with later submission of acceptable efficacy data.