

US EPA ARCHIVE DOCUMENT

EFFICACY REVIEW

DATE: April 19, 2006

FILE SYMBOL: PROMERIS SPOT ON FOR DOGS
EPA File Symbol 80490-E

DP BARCODE: D311483

CHEMICAL NUMBER: CAS No. 35037-73-1

REGISTRANT: Fort Dodge Animal Health

GLP: No

CHEMICAL: Metaflumizone (14.34%), Amitraz (14.34%)

PURPOSE: Provide efficacy data to support product registration of a spot-on for control of fleas and ticks on dogs and puppies over eight weeks of age.

MRID:

463965813. J. Hair and D. Rugg. 2004. Dose Confirmation of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs. Project Number 0817-C-US-01-03; Performing Laboratory Nu-Era Farms, Stillwater, OK, Sponsor Fort Dodge Animal Health, Princeton, NJ. 57 p. (GLP with certain deviations)

46395814. R. Everett, J. Cunningham and D. Rugg 2004. Efficacy of a Topically Applied Spot-On Formulations of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs. Project Number 0817-C-US-04-03; Performing Laboratory AgResearch Consultants, Greenbrier, AR; Sponsor Fort Dodge Animal Health, Princeton, NJ. 61 p. (GLP with certain exceptions)

46395815. R. Everett, J. Cunningham and D. Rugg 2004. Effects of Shampooing or Water Immersion on the Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs. Project Number 0817-C-US-05-03; Performing Laboratory AgResearch Consultants, Greenbrier, AR; Sponsor Fort Dodge Animal Health, Princeton, NJ. 63 p. (GLP with certain exceptions)

46395816. J. Hair and D. Rugg 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Deer Ticks on Dogs. Project Number 0817-C-US-06-03; Performing Laboratory Nu-Era Farms, Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. 42 p. (GLP with certain deviations)

46395817. L. Carter and D. Rugg 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Deer Ticks on Dogs. Project Number 0817-C-US-07-03; Performing Laboratory Stillmeadow Inc., Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. 50 p. (GLP with certain deviations)

46395818. J. Hair and D. Rugg 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs Exposed to Outdoor Conditions; Project Number 0817-C-US-08-03; Performing Laboratory Nu-Era Research Farms, Stillwater, OK; Sponsor: Fort Dodge Animal Health, Princeton, NJ. 43 p. (GLP with certain deviations)

46395819. R. Everett and D. Rugg 2004. Evaluation of Repeat Applications of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz on Dogs. Project Number 0817-C-US-11-04; Performing Laboratory Nu-Era Research Farms, Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. 54 p. (GLP with certain deviations)

46395820. J. Hair and D. Ruff 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Lone Star Ticks on Dogs. Project Number 0817-C-US-11-04; Performing Laboratory Nu-Era Research Farms, Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. 39 p. (GLP with certain deviations)

TEAM REVIEWER: John Hebert

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BACKGROUND:

The product “Promeris Spot On For Dogs” is intended for continuous control and prevention of fleas and ticks on dogs and puppies over eight weeks of age. The directions for use state to apply the material as a single spot to the skin between the shoulder blades. For dogs/puppies ≤ 11 lb the rate is 0.023 fl oz (0.8 ml); for 11-22 pounds the rate is 0.045 fl. oz; for 22-56 pounds the rate is 0.113 fl. oz; for 56-89 pounds the rate is 0.18 fl. oz; and for 89-111 pounds the rate is 0.225 fl oz.

Label claims include:

“Full month protection with a single treatment”, “controls fleas and ticks for at least one month.”

“Rapidly kills adult fleas which may cause dermatitis.”

“Waterproof”

“It may also be used to prevent infestation in flea free animals being taken into a flea contaminated environment.”

“Controls/kills brown dog ticks, American dog ticks, lone star ticks, and black-legged or deer ticks that can transmit Lyme disease.”

“”fast-acting, rapid-control.”

“Product resists the effects of water and remains effective even if the dog is exposed to sunlight.”

DATA REVIEW:

A summary of the results of the submitted data is provided below.

1. **463965813. J. Hair and D. Rugg 2004. Dose Confirmation of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs. Project Number 0817-C-US-01-03; Performing Laboratory Nu-Era Farms, Stillwater, OK, Sponsor Fort Dodge Animal Health, Princeton, NJ. (GLP with certain deviations)**

An experiment was conducted to determine the efficacy of three dose levels of R-28153/amitraz in a spot-on formulation against cat fleas (*Ctenocephalides felis*) and brown dog ticks (*Rhipicephalides sanguineus*) infesting adult female beagle dogs. Dogs weighed from 9.3 to 16.6 kg. The rates were 0.5X (0.067 ml/kg bw), 1X (0.134 ml/kg bw) and 2X (0.268 ml/kg bw) the proposed minimum commercial rate. The product was compared to a positive control (Frontline, EPA Reg. No. 65331-3, 10% fipronil), an untreated control and a vehicle-treated control. There were six animals per treatment group. Dogs were housed in individually.

Treatment:

day -7 each dog was infested with 50 ticks
day -6 each dog was infested with 100 unfed cat fleas
day -5 each dog was examined and combed to remove and count the flea and ticks
day -2 each dog was infested with 50 ticks
day -1 each dog was infested with 100 unfed cat fleas
day 0 each dog was treated (dose was based on day -2 body weights); single spot between the shoulder blades
day 1 approx. 24 hrs after treatment dogs were examined and “finger count” conducted (qualitative assessment of the numbers of live ticks and fleas observed during a 5 minute period)
day 2 each dog was examined and combed to remove and count fleas and ticks

Using this procedure, dogs were reinfested with ticks on days 5, 12, 19, 26, 33 and 40, and with fleas on days 6, 13, 20, 27, 34 and 41. Observations were made on days 7, 14,

21, 28, 35 and 42. To increase chances of successful tick attachment, dogs were held in tick infestation chambers for about 8 hours after applying ticks.

Reported results:

Table 1. Results for Dose Test (Cat Fleas and Brown Dog Ticks)

Fleas	Results
0.5X	>90% from day 2 to day 28
1X	>90% from day 2 to day 42
2X	>90% from day 2 to day 35
Frontline	>90% from day 2 to day 42
Ticks	
0.5X	>90% from day 2 to day 21
1X and 2X	>90% from day 2 to day 35
Frontline	>90% from day 2 to day 35

- 46395814. R. Everett, J. Cunningham and D. Rugg 2004. Efficacy of a Topically Applied Spot-On Formulations of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs. Project Number 0817-C-US-04-03; Performing Laboratory AgResearch Consultants, Greenbrier, AR; Sponsor Fort Dodge Animal Health, Princeton, NJ. (GLP with certain exceptions)**

An experiment was conducted to determine the efficacy of the proposed commercial rate of R-28153/amitraz in a spot-on formulation against cat fleas (*Ctenocephalides felis*) and brown dog ticks (*Rhipicephalides sanguineus*) infesting adult female beagle dogs. Dogs weighed from 5.5 to 30.6 kg. The proposed commercial rates were: <4.5 kg, 0.6 ml; 4.6-10.5 kg, 1.4 ml; 10.6-25.5 kg, 3.4 ml; 25.6-60 kg, 8 ml. The product was compared to a positive control (Frontline, EPA Reg. No. 65331-5, 10% fipronil/9% s-methoprene), an untreated control, and a vehicle control. There were eight animals per treatment group. For the R-28153/amitraz product, six dogs were treated at 3.4 ml, and 2 dogs were treated at 1.4 ml. Dogs were housed individually.

Treatment:

- day -7 each dog was infested with 50 adult brown dog ticks
- day -6 each dog was infested with 100 unfed cat fleas
- day -5 each dog was examined and combed to remove and count the flea and ticks
- day -2 each dog was infested with 50 adult brown ticks and 50 American dog ticks
- day -1 each dog was infested with 100 unfed cat fleas
- day 0 each dog was treated (dose was based on day -2 body weights); single spot between the shoulder blades
- day 1 approx. 24 hrs after treatment dogs were examined and "finger count" conducted (qualitative assessment of the numbers of live ticks and fleas observed during a 5 minute period)
- day 2 each dog was examined and combed to remove and count fleas and ticks

Using this procedure, dogs were reinfested with ticks on days 5, 12, 19, 26, 33 and 40, and with fleas on days 6, 13, 20, 27, 34 and 41. Observations were made on days 7, 14, 21, 28, 35 and 42.

Reported results:

Table 2. Results for Dose Test (Cat Fleas and Brown Dog Ticks)

Fleas	Results
R-28153/amitraz	>90% from day 1 to day 35; 86.6% on day 42
Frontline	>90% from day 1 to day 42
Ticks	Results
R-28153/amitraz	>90% from day 1 to day 21; 89.8% on day 28
Frontline	>90% from day 1 to day 28; 70.1% on day 35

3. **46395815. R. Everett, J. Cunningham and D. Rugg 2004. Effects of Shampooing or Water Immersion on the Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs. Project Number 0817-C-US-05-03; Performing Laboratory AgResearch Consultants, Greenbrier, AR; Sponsor Fort Dodge Animal Health, Princeton, NJ. (GLP with certain exceptions)**

An experiment was conducted to determine the efficacy of the proposed commercial rate of R-28153/amitraz in a spot-on formulation against cat fleas (*Ctenocephalides felis*) and brown dog ticks (*Rhipicephalides sanguineus*) infesting mixed breed dogs following weekly simulated exposure to rain and swimming or after shampooing at 14 days post-treatment. Dogs weighed from 4.7 to 19.3 kg. The proposed commercial rates were: 4.6-10.5 kg, 1.4 ml and 10.6-25.5 kg, 3.4 ml. Dogs were housed individually. There were four treatment groups (six dogs per group):

1. Control (water immersion only)
2. Commercial rate, water immersion
3. Control, shampoo
4. Commercial rate, shampoo.

Treatment:

- day -7 each dog was infested with 50 adult brown dog ticks
- day -6 each dog was infested with 100 unfed cat fleas
- day -5 each dog was examined and combed to remove and count the flea and ticks
- day -2 each dog was infested with 50 adult brown ticks and 50 American dog ticks
- day -1 each dog was infested with 100 unfed cat fleas
- day 0 each dog was treated (dose was based on day -2 body weights); single spot between the shoulder blades
- day 2 each dog was examined and combed to remove and count fleas and ticks

Using this procedure, dogs were reinfested with ticks on days 5, 12, 19, 26, 33 and 40, and with fleas on days 6, 13, 20, 27, 34 and 41. The dogs (with water immersion) were observed (examined, combed and parasite counted) on days 7, 14, 21, 28, 35 and 42. The dogs (with shampooing) were observed on days 7, 14, 21, 29, 36 and 43 (also “finger-counted” on day 28). The dogs (with water immersion) were immersed in a warm water 100-gallon tank 3/4 full. Dogs were held in the water 20-30 seconds, and during this time water was splashed on the head three times to thoroughly wet the head. This procedure was done on days 2, 9, 16 and 23. The dogs (with shampooing) were shampooed with Allergroom^R shampoo. The shampoo was massaged/lathered on dog’s wetted coat, then left on for 5 minutes, then thoroughly rinsed (on day 14).

Reported results:

Table 3. Results for shampooing/water immersion test.

Fleas	Results
water immersion	>90% on all count days to day 35; 89.6% on day 42
following shampooing	days 21 and 28 was 89.3 and 88.1% respectively;; >90% on days 29 and 36, declining to 72.7% on day 43.
Ticks	
water immersion	>90% on all count days to day 35; 84% on day 42
following shampooing	79.3% on the 1st count day after shampooing (day 21) and 69.7% on day 29.

The study authors concluded swimming or rainfall exposure is unlikely to affect flea/tick control. Also, shampooing 2 weeks after treatment is unlikely to affect control, although it may reduce efficacy of the product against ticks. The authors reported there were no unexpected adverse effects that could be attributable to treatment.

4. **46395816. J. Hair and D. Rugg 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Deer Ticks on Dogs. Project Number 0817-C-US-06-03; Performing Laboratory Nu-Era Farms, Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. (GLP with certain deviations)**

An experiment was conducted to determine the efficacy of three dose levels of R-28153/amitraz in a spot-on formulation against cat fleas (*Ctenocephalides felis*) and deer ticks (*Ixodes scapularis*) infesting adult female beagle dogs. Dogs weighed from 9.65 to 16.1 kg. Eight dogs were tested at the proposed commercial rate (each dog received 3.4 mL based on body weights). Eight dogs were untreated. Dogs were housed individually.

Treatment:

day -9 each dog was infested with 50 ticks
 day -8 each dog was infested with 100 unfed cat fleas
 day -7 each dog was examined and combed to remove and count the flea and ticks
 day -2 each dog was infested with 50 ticks
 day -1 each dog was infested with 100 unfed cat fleas
 day 0 each dog was treated (dose was based on day -2 body weights); single spot between the shoulder blades
 day 2 each dog was examined and combed to remove and count fleas and ticks

Using this procedure, dogs were reinfested with ticks on days 5, 12, 19, 26, 33 and 40, and with fleas on days 6, 13, 20, 27, 34 and 41. Observations were made on days 7, 14, 21, 28, 35 and 42.

Reported results:

Table 4. Results for Dose Test (Cat Fleas and Deer)

Fleas	Results
Commercial rate	>90% from treatment to day 28; 88% at day 35, 78% on day 42
Deer Ticks	
Commercial Rate	>90% on all counts from treatment to day 21; days 28, 35 and 42, it was 82%, 79% and 71%, respectively.

5. **46395817 L. Carter and D. Rugg 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Deer Ticks on Dogs. Project Number 0817-C-US-07-03; Performing Laboratory Stillmeadow Inc., Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. (GLP with certain deviations)**

An experiment was conducted to determine the efficacy of the proposed commercial rate of R-28153/amitraz in a spot-on formulation against cat fleas (*Ctenocephalides felis*) and brown dog ticks (*Rhipicephalus sanguineus*) infesting adult male and female beagle dogs. Dogs weighed from 8.6 to 14 kg. Eight dogs were treated at the proposed commercial rates (3.4 mL or 1.4 depending on weight), and eight dogs were untreated. Study design was similar to previous studies by this lab.

Reported results:

Table 5. Results for Dose Test (Cat Fleas and Brown Dog Ticks Based on Geometric means

Fleas	Results
Commercial rate	>90% from treatment (counts started on day 2) to day 35; 90% on day 42
Brown Dog Ticks	

Commercial Rate	>90% on all counts from treatment on days 7, 14, 21 and 35; on days 2, 28 and 42 it was 85.8, 82.3 and 59.5% respectively.(counts started on day 2) to day 21; days 28, 35 and 42, it was 88%, 79% and 56%, respectively.
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The authors concluded that treatment with R-28153/amitraz spot-on provided at least 4 weeks control of both species.

6. **46395818. J. Hair and D. Rugg. 2004 Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Fleas and Ticks on Dogs Exposed to Outdoor Conditions; Project Number 0817-C-US-08-03; Performing Laboratory Nu-Era Research Farms, Stillwater, OK; Sponsor: Fort Dodge Animal Health, Princeton, NJ. 43 p. (GLP with certain deviations)**

An experiment was conducted to determine the efficacy of the proposed commercial rates of R-28153/amitraz in a spot-on formulation against cat fleas and brown dog ticks infesting adult male and female beagle dogs, which had been exposed to outdoor conditions (outdoor runs on Bermuda grass; some shelter provided by a lean-to-house) for a period of two hours per day.

Eight dogs were treated at the proposed commercial rate (four dogs received 3.4 mL and four dogs received 1.4 mL based on body weights). Eight dogs were untreated. The study design followed that of MRID 46395819 (with small variations, e.g., some of the observation days were different).Results:

Table 6. Results for dogs exposed to outdoor conditions.

Fleas	Results
Commercial rate	>90% from treatment day to day 14 when assessed at 24 hrs post-treatment; 80.9% on day 21 at 24 hrs post-treatment; >90% on day 28, 86.8% on day 35 and 78% on day 42 based on 48-hr post-treatment counts
Brown Dog Ticks	
Commercial Rate	>90% on all counts from treatment to days 7, 14, 21 and 35. On days 2, 28 and 42, control was 85.8, 82.3 and 59.5%, respectively

7. **46395819. R. Everett and D. Rugg 2004. Evaluation of Repeat Applications of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz on Dogs. Project Number 0817-C-US-11-04; Performing Laboratory Nu-Era Research Farms, Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. 54 p.(GLP with certain deviations)**

This study was conducted to examine the safety of (four) repeated monthly applications of the proposed product to dogs. Efficacy was also evaluated against flea and tick challenges after each treatment. Study not examined, since the purpose of the study was

to assess general animal safety (should be part of the domestic animal safety review).

8. **46395820. J. Hair and D. Ruff 2004. Efficacy of a Topically Applied Spot-on Formulation of R-28153 Combined With Amitraz Against Lone Star Ticks on Dogs. Project Number 0817-C-US-11-04; Performing Laboratory Nu-Era Research Farms, Stillwater, OK, Sponsor: Fort Dodge Animal Health, Princeton, NJ. 39 p. (GLP with certain deviations)**

An experiment was conducted to determine the efficacy of the proposed commercial rate of R-28153/amitraz in a spot-on formulation against lone star ticks (*Amblyomma americanum*) infesting adult beagle dogs. Dogs weighed from 7.25 to 15.9 kg. There were eight animals in the treatment group and eight animals in the control group. For the R-28153/amitraz treatment, one dog was treated at 1.33 mL and 7 dogs were treated at 3.33 ml. Dogs were housed individually.

Treatment:

day 0 each dog was treated

day 2 each dog was examined and combed to remove and count fleas and ticks

Using this procedure, dogs were reinfested on days 5, 12, 19, 26, 33 and 40. Observations were made on days 7, 14, 21, 28, 35 and 42.

Reported results:

Table 7. Results for Lone Star Ticks

Lone Star Ticks	Results
R-28153/amitraz	>90% on days 7, 14, 21 and 35; on days 2, 28 and 42, efficacy was 84.3%, 75.6% and 74.9%, respectively on day 1 to day 35; 86.6% on day 42

The authors reported that presence of unattached ticks may have minimized the potential efficacy of the treatment, and would expect up to 5 weeks control of lone star ticks. Live ticks collected from treated dogs on day 28 and 35 were not attached; ticks recovered from dogs on day 42 were attached (ticks on control dogs were attached on all count days). The authors reported no unexpected adverse effects that could be attributable to treatment.

RECOMMENDATIONS:

The submitted efficacy data support the use of Promeris Spot On for Dogs for the control of fleas and ticks (including brown dog ticks, American dog ticks, lone star ticks, and black-legged or deer ticks that can transmit Lyme disease) on dogs and puppies over eight weeks of age.

The following label recommendations apply:

1. Delete the claim “This product remains effective even if the dog is exposed to sunlight.” The submitted report (MRID 46395818) does not support this claim because (1) daily weather conditions were not reported, and (2) dogs had access to shelter.
2. The directions for use must be revised so the applicator understands what dose to apply to a dog weighing 11 pounds, 22 pounds, 56 pounds and 89 pounds.

[Note to PM: MRID 46395819 is a study on the evaluation of repeat applications on dogs, and its purpose was to assess general animal safety. This study should be part of the domestic animal safety review.]