EFFICACY REVIEW

PRODUCT:	SVP7
REG #:	83399-6
DATE:	10/4/10
GLP:	Variable
BARCODE:	D380592
DECISION:	436849
CHEMICALS:	Permethrin (36.08%) Pyriproxyfen (0.44%) Dinotefuran (4.95%)
CHEMICAL NUMBERS:	109701, 129032, 044312
PURPOSE:	Review data to support efficacy claims.
MRIDS:	*48144401. Fourie, J. (2010) The Effects of Weekly Shampooing on the Persistent Efficacy of Vectra 3D Against Ticks (Rhipicephalus sanguineus) and Fleas (Ctenocephalides felis) on Dogs. Project Number: SVP09002, CV/09/666. Unpublished study prepared by Clin Vet International. 66 p.* *48144402. Fourie, J. (2010) Efficacy of Vectra 3D Against Stomoxys calcitrans on Dogs: SVP7. Project Number: SVP09004, CV/09/659. Unpublished study prepared by Clin Vet International. 40 p.* *48144403. Fourie, J. (2009) Comparative Study on the Efficacy of Three Topically Applied Products Against Fleas (Ctenocephalides felis) on Dogs. Project Number: SVP08022, CV/08/541. Unpublished study prepared by Clin Vet International. 53 p.* *48144404. Fourie, J. (2009) Comparative Study on the Efficacy of Three Topically Applied Products Against Ticks (Rhicephalus sanguineus) on Dogs: (SVP7). Project Number: SVP08023, CV/08/542. Unpublished study prepared by Clin Vet International. 69 p.*

48144405. Conti, J. (2010) Comparative Efficacy – Fire Ants/Mites: (SVP7). Project Number: SVP/JAC/7/22010. Unpublished study prepared by Summit VetPharm, LLC. 28 p.

TEAM REVIEWER: Rita Kumar

EFFICACY REVIEWER: Jennifer Urbanski, Entomologist 10/4/10

SECONDARY EFFICACY REVIEWER: Kable Bo Davis, Entomologist 10/4/10

BACKGROUND:

SVP7 (Registration Number 83399-6) is a spot-on topical pesticide intended for the treatment and prevention of fleas, ticks, mosquitoes, lice, mites, and biting flies on dogs and puppies 7 weeks and older. The proposed label includes the alternate brand name Vectra 3D. The application rate varies per weight class of dog. The directions for use state to reapply every month or as recommended by a physician. The following list includes examples of newly proposed claims found on the pending label:

- "*Prevents fly strike*"
- "*Repels (and kills) (annoying) (bothersome) (nuisance) biting flies*"
- "*Kills bedbugs*"
- "*Repelled flies and mosquitoes quickly leave and don't bite*"
- "*Helps dogs stay healthy and comfortable by controlling parasites*"
- "*Controls all fly life stages*"
- "*Continues to work after multiple shampooing*"
- "*Repels fire ants*"
- "*Reduces flea feeding within 5 minutes*"

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.

48144401. Fourie, J. (2010) The Effects of Weekly Shampooing on the Persistent Efficacy of Vectra 3D Against Ticks (*Rhipicephalus sanguineus*) and Fleas (*Ctenocephalides felis*) on Dogs. Project Number: SVP09002, CV/09/666. Unpublished study prepared by Clin Vet International. 66 p.

The objective of this study was to determine the effects of weekly shampooing with three commercially available shampoos and a specially formulated non-

ionic/amphoteric shampoo on the efficacy of Vectra 3D® against a tick (*Rhipicephalus sanguineus*) and a flea (*Ctenocephalides felis*). The experimental design consisted of dividing 40 dogs into five groups of eight dogs (24 females, 16 males; one control group, four treatment groups in which each is treated with a different shampoo). All dogs were determined to be healthy and ranged in weight from 11.0 to 20.8 kg. They were acclimated to the experimental housing seven days prior to Vectra 3D® treatment. Dogs from four of the five groups (i.e. the treatment groups) were treated with Vectra 3D® on day 0 (Table 1). These groups were shampooed on days 6, 13, 20 and 27. The control group was not treated with Vectra 3D® and was not shampooed. All dogs were infested with ~100 unfed fleas on days -6, -2, 8, 15, 22, and 29, and 50 unfed ticks on days -2, 7, 14, 21, and 28. Flea and tick counts were performed on days -5 (fleas only), 2, 9, 16, 23, and 30. Percent efficacy was determined after each count and was calculated as 100 X ((geometric mean of live ticks or fleas in the control group – geometric mean of live fleas or ticks in the treatment group) / geometric mean of live ticks or fleas in the control group). Efficacy based on arithmetic means was also calculated but data will not be shown here.

Table 1. Experimental design

STUDY PROCEDURE	**Vectra 3D Application**	**Shampooing**	**Tick Infestation**	**Flea Infestation**	**Tick/Flea Counts**
GROUP(S)	Treatment	Treatment	All	All	All
DAYS	0	6, 13, 20, 27	-2, 7, 14, 21, 28	-6, -2, 8, 15, 22, 29	-5 (fleas only), 2, 9, 16, 23, 30

Results-

Table 2. Efficacy percentages for ticks and fleas

Day	Ticks				Fleas			
	Shampoo 1	Shampoo 2	Shampoo 3	Shampoo 4	Shampoo 1	Shampoo 2	Shampoo 3	Shampoo 4
2[a]	59.4	87.8	52.7	57.3	100.0	99.9	100.0	100.0
9	98.0	98.0	99.0	99.3	90.9	98.1	96.8	99.5
16	87.0	91.3	92.6	94.4	95.6	98.2	96.5	97.8
23	70.7	77.6	86.3	80.9	55.8	82.7	85.6	79.6
30	58.6	62.3	34.9	51.7	73.8	91.6	84.4	81.4

[a]First shampooing did not occur until day 6.

Two days after Vectra 3D® treatment but before the first shampooing, efficacies of the four treatment groups ranged from 52.7-87.8% for ticks and 99.9-100% for fleas (Table 2). Sixteen days after Vectra 3D® treatment after shampooing twice, efficacies were >90% for all treatments in both fleas and ticks, with the exception of one treatment which had an efficacy of 87% for ticks. Efficacies dropped below 90% three and four weeks post-treatment after shampooing 3-4 times for all treatments, with the exception of one treatment which had an efficacy of 91.6% for fleas.

48144402. Fourie, J. (2010) Efficacy of Vectra 3D Against Stomoxys calcitrans on Dogs: SVP7. Project Number: SVP09004, CV/09/659. Unpublished study prepared by Clin Vet International. 40 p.

The objective of this study was to determine the efficacy of Vectra 3D® treatment against bloodfeeding and mortality of *Stomoxys calcitrans* on dogs. The experimental design consisted of dividing 20 dogs into two groups of ten (control and treatment). All dogs were determined to be healthy and ranged in weight from 10.9 to 20.96 kg. They were acclimated to the experimental housing seven days prior to Vectra 3D® treatment. Dogs from the treatment group were treated with Vectra 3D® on day 0. Both control and treatment dogs were infested with ~25 flies on days -4, 1, 8, 15, 22, and 29. Thirty minutes after infestation, live, dead, and moribund flies were collected and bloodfeeding status was recorded. Flea and tick counts were performed on days -5 (fleas only), 2, 9, 16, 23, and 30. Percent efficacy for blood feeding was determined after each count and was calculated as (100 X ((geometric mean of flies that took a blood meal in the control group – geometric mean of flies that took a blood meal in the treatment group) / geometric mean of flies that took a blood meal in the control group)). Percent efficacy for mortality was determined after each count and was calculated as (100 X ((geometric mean of live flies in the control group – geometric mean of live flies in the treatment group) / geometric mean of live flies in the control group)). Efficacy based on arithmetic means was also calculated but data will not be shown here.

Results-

Table 3. Efficacies (%) for bloodfeeding prevention and mortality in *Stomoxys calcitrans*

Day	Bloodfeeding	Mortality
1	93.9	93.4
8	94.7	93.7
15	98.6	94.8
22	98.7	96.7
29	78.9	84.7

Three weeks after Vectra 3D® treatment, *Stomoxys calcitrans* bloodfeeding prevention and mortality ranged from 93.9-98.7% and 93.4-96.7%, respectively (Table 3). Efficacies dropped to 78.9% for bloodfeeding prevention and 84.7% for mortality four weeks post-treatment.

48144403. Fourie, J. (2009) Comparative Study on the Efficacy of Three Topically Applied Products Against Fleas (*Ctenocephalides felis*) on Dogs. Project Number: SVP08022, CV/08/541. Unpublished study prepared by Clin Vet International. 53 p.

The objective of this study was to compare the efficacies of three spot-on products (Vectra 3D®, K9 Advantix®, and Frontline® Plus) against fleas (*Ctenocephalides felis*) on dogs. The experimental design consisted of dividing 64 dogs (32 males, 32 females) into four groups (control and three treatments). Each group was divided into subgroups (referred to as "a" and "b"; 8 dogs per subgroup). All dogs were determined to be

healthy and ranged in weight from 10.78-18.74 kg. They were acclimated to the experimental housing seven days prior to treatment. Dogs from the three treatment groups were treated with either Vectra 3D®, K9 Advantix®, or Frontline® Plus on day 0. Both control and treatment dogs were infested with ~100 fleas on days -6, -2, 7, 14, 21 and 28. After treatment, efficacy was assessed on the same day as infestation, either two hours post-infestation (subgroups "a") or six hours post-infestation (subgroups "b"). Percent efficacy for mortality was determined after each count and was calculated as (100 X ((geometric mean of live fleas in the control group – geometric mean of live fleas in the treatment group) / geometric mean of live fleas in the control group)). Efficacy based on arithmetic means was also calculated but data will not be shown here.

Results-

Table 4: Efficacies (%) against *Ctenocephalides felis*

Day	2 hours post-infestation			6 hours post-infestation		
	Vectra 3D	K9 Advantix	Frontline Plus	Vectra 3D	K9 Advantix	Frontline Plus
0	57.1	14.2	30.1	97.2	94.6	25.1
7	99.7	99.6	93.8	100.0	100.0	100.0
14	99.7	100.0	95.0	100.0	100.0	100.0
21	99.9	100.0	77.4	100.0	100.0	98.5
28	97.7	99.2	72.4	99.3	99.2	94.1

When efficacy was calculated 2 hours post-infestation, Vectra 3D and K9 Advantix had >90% efficacy during all four weeks of the experiment, while Frontline Plus had efficacies >90% for only the first two weeks post-treatment (Table 4). When efficacy was calculated 6 hours post-infestation, all three treatments had >90% efficacy during all four weeks of the experiment. For the two hour assessments, there was a statistical difference in mean number of fleas between Vectra 3D and Frontline Plus on days 7, 14, 21 and 28, while there was no difference between Vectra 3D and K9 Advantix. For the 6 hour assessments, there was a statistical difference in mean number of fleas between Vectra 3D and Frontline Plus on days 0, 21 and 28, while there was no difference between Vectra 3D and K9 Advantix.

48144404. Fourie, J. (2009) Comparative Study on the Efficacy of Three Topically Applied Products Against Ticks (*Rhicephalus sanguineus*) on Dogs: (SVP7). Project Number: SVP08023, CV/08/542. Unpublished study prepared by Clin Vet International. 69 p.

The objective of this study was to compare the efficacies of three spot-on products (Vectra 3D®, K9 Advantix®, and Frontline® Plus) against ticks (*Rhicephalus sanguineus*) on dogs. The experimental design consisted of dividing 32 dogs (16 males, 16 females) into four groups (control and three treatments). All dogs were determined to be healthy and ranged in weight from 10.8 -18.4 kg. They were acclimated to the experimental housing seven days prior to treatment. Dogs from the three treatment groups were treated with either Vectra 3D®, K9 Advantix®, or Frontline® Plus on day 0. Both control and treatment dogs were infested with ~50 ticks on days -8, -2, 7, 14, 21 and

28. After treatment, efficacy was assessed 24- and 48-hours after infestation. Percent efficacy against ticks was determined after each count and was calculated as (100 X ((geometric mean of live fleas in the control group – geometric mean of live fleas in the treatment group) / geometric mean of live fleas in the control group)). Efficacy based on arithmetic means was also calculated but data will not be shown here.

Table 5. Efficacies (%) against *Rhicephalus sanguineus*

Day of Infestation	24 hrs post-infestation			48 hrs post-infestation		
	Vectra 3D	K9 Advantix	Frontline Plus	Vectra 3D	K9 Advantix	Frontline Plus
0	11.9	16.7	10.7	57.1	54.3	75.5
7	99.6	99.2	94.1	99.6	99.6	99.0
14	98.8	96.9	95.3	100.0	98.3	99.6
21	98.1	95.1	81.7	99.7	95.4	95.0
28	96.7	91.7	58.6	98.5	92.8	91.8

When efficacy was calculated 24 hours post-infestation, Vectra 3D and K9 Advantix had >90% efficacy during all four weeks of the experiment, while Frontline Plus had efficacies >90% for only the first two weeks post-treatment (Table 5). When efficacy was calculated 48 hours post-infestation, all three treatments had >90% efficacy during all four weeks of the experiment. For the 24 hour post-infestation assessments, there was a statistical difference in mean number of fleas between Vectra 3D and Frontline Plus on days 8, 22 and 29, while there was no difference between Vectra 3D and K9 Advantix. For the 48 hour post-infestation assessments, there was a statistical difference in mean number of fleas between Vectra 3D and Frontline Plus on days 23 and 30, and between Vectra 3D and K9 Advantix on day 23.

48144405. Conti, J. (2010) Comparative Efficacy – Fire Ants/Mites: (SVP7). Project Number: SVP/JAC/7/22010. Unpublished study prepared by Summit VetPharm, LLC. 28 p.

The above study is comprised of five separate documents, each of which will be individually addressed.

Costa, H. S., L. Greenberg, J. Klotz, and M. K. Rust. (2005) Response of Argentine Ants and Red Imported Fire Ants to permethrin-impregnated plastic strips: foraging rates, colonization of potted soil, and differential mortality. Journal of Economic Entomology 98 (6):2089-2094.

While this study establishes that exposure of red imported fire ants and Argentine ants to permethrin-impregnated plastic results in significant mortality in as little as one minute, this data is not relevant to Vectra 3D, as it is a spot-on product which has a different mode of exposure.

Fire Ant Control Methods Around Pets, by Drs. Foster and Smith

This informational sheet does not contain any information about spot-ons and is therefore not relevant to this efficacy review.

Twenty Questions About Fire Ants, by K. Loftin and J. Hopkins

This informational sheet does not contain any information about spot-ons and is therefore not relevant to this efficacy review.

Hansen, O., N, Mencke, K. Pfister, and W. Beck. (2006) Efficacy of a formulation containing imidacloprid and permethrin against naturally acquired ectoparasite infestations (Ctenocephalides felis, Cheyletiella parasitovorax, and Listrophorus gibbus) in rabbits. Intern J Appl Res Vet Med 4 (4): 320-325.

This article is not relevant to Vectra 3D because the study is performed in rabbits, not dogs, and it is testing a formulation containing both permethrin and imidacloprid, whereas Vectra 3D contains permethrin, pyriproxyfen, and dinotefuran.

Birke, L. L., P. E. Molina, D. G. Baker, S. T. Leonard, L. J. Marrero, M. Johnson, and J. Simkin. (2009) Comparison of selamectin and imidacloprid plus permethrin in eliminating Leporacarus gibbus infestation in laboratory rabbits (oryctolagus cuniculus). Journal of the American Association for Laboratory Animal Science 48 (6):757-762.

This article is not relevant to Vectra 3D because the study is performed in rabbits, not dogs, and it is testing a formulation containing either selamectin or both permethrin and imidacloprid, whereas Vectra 3D contains permethrin, pyriproxyfen, and dinotefuran.

RECOMMENDATIONS:

The submitted data are not adequate to retain claims for the control of bedbugs or fire ants. Furthermore, while the claim for control of biting flies is substantiated, this is only the case for three weeks, not four. The following changes are required:

1. Throughout label, change all "*pet*" references to read "*dog*", as the product is not intended for all pets.

2. Throughout the label, delete all references to bedbugs. Claims for bed bugs are not appropriate for spot-ons.

3. Throughout the label, delete all references to fire ants. Claims for fire ants are not appropriate for spot-ons.

4. Throughout the label, change references to "*mites*" to read "*mites (excluding mange mites)*".

5. Throughout the label, claims control of life cycle are acceptable but direct "pupae" claims are not.

6. Given the above two changes, using the terms "*7 way protection*" and "*8 way protection*" are not allowed, as bed bugs and fire ants are not to be included on the label and therefore this would imply heightened efficacy.

7. Throughout the label, change all references to "*flies*" to specify the type of fly (either sand fly or biting fly), as efficacy is needed from three species of fly (house fly, one species of biting fly, and one species of choice) for a general fly claim.

8. On page 6, change "*Kills fleas in 6 hours*" to read "*Starts to kill fleas in 6 hours*".

9. On page 6, change "*Quick onset of activity kills fleas within 2 hours*" to read "*Starts to kill fleas within 2 hours*".

10. On page 8, change "*Regular use kills (controls) all stages of the flea life cycle*" to read "*Monthly use kills (controls) all stages of the flea life cycle*".

11. On page 8, change "*Regular use (of SVP7) breaks the flea life cycle*" to read "*Monthly use (of SVP7) breaks the flea life cycle*".

12. On page 8, delete "*Recommended for use in an integrated flea management system*". Alternatively, clearly define "an integrated flea management system".

13. On page 9, change "*Easy effective control of fleas, ticks and mosquitoes*" to read "*Effective control of fleas, ticks and mosquitoes*".

14. On page 9, delete "*Long lasting flea, tick and mosquito control for your pet*". Alternatively, define "long lasting" and change "*pet*" to "*dog*".

15. On page 9, change "*SVP7 repels and kills fleas, ticks, mosquitoes before they bite*" to read "*SVP7 repels and kills fleas, ticks, mosquitoes*", as the original statement implies heightened efficacy.

16. On page 10, delete "*(SVP7) prevents flea and tick attachment*", as this implies heightened efficacy.

17. On page 10, delete "*SVP7 inhibits (flea) (and tick) feeding*", as this implies heightened efficacy.

18. On page 11, change "*Stops existing flea infestations by rapidly killing adult fleas*" to read "*Stops existing flea infestations by killing adult fleas*".

19. On pages 11 and 12, delete the claims, "*Prevents fly strike*", "*Controls fly strike*", and "*Reduces fly strike*".

20. On page 12, change "*Repellency against fleas, ticks, mosquitoes, lice, mites, biting flies, bedbugs and fire ants for 4 weeks (30 days) (one month)*" to read "*Repellency against fleas, ticks, mosquitoes, lice, and mites (excluding mange mites) for 4 weeks (30 days) (one month)*", as Vectra 3D showed an efficacy of >90% against the biting house fly for only three weeks.

21. On page 12, delete the claims, "*Repelled flies and mosquitoes quickly leave and don't bite*" and "*Repelled flies and mosquitoes don't bite*", as this implies heightened efficacy.

22. On page 12, delete the claim, "*Helps dogs stay healthy and comfortable by controlling parasites*", as this implies heightened safety.

23. On page 12, delete the claim, "*Eliminates infestations of chewing lice*", as the term "eliminates" signifies heightened efficacy.

24. On page 12, delete the claim, "*SVP7 may be helpful in providing an extra layer of protection against infection with heartworm larvae from feeding mosquitoes*", as this implies heightened safety.

25. On page 12, delete the claim "*Controls all fly life stages*".

26. On page 12, delete the claim "*Controls aggressive feeding by flies*".

27. On page 12, delete the claims, "*Continues to work after multiple shampooing*", "*Continues to repel and kill fleas, ticks, biting flies, and mosquitoes after multiple shampooing*", and "*Continues to kill and repel fleas and ticks after multiple shampooing*". The first two claims include pests for which data was not submitted. The third claim implies heightened efficacy, as the data show that the product is only effective after two shampooings.

28. On page 12, change "*Helps to relieve your dogs discomfort by controlling fleas, ticks, mites, (biting) flies, bedbugs and lice infestations*" to read "*Helps to relieve your dogs discomfort by controlling fleas, ticks, mites (excluding mange mites), biting flies, and lice infestations*".

29. On page 12, delete the claim "*Kills and repels mosquitoes which may carry West Nile virus*".

30. On page 12, delete the claim "*Stops and controls infestations of chewing lice and Domestic mange mites*".

31. On page 12, change "*Kills the vectors that may transmit Lyme disease, Rocky Mountain spotted fever, babesiosis, ehrlichiosis, bartonellosis, hepatozoonosis, leishmaniasis, tularemia and heartworm disease*" to read "*Kills the listed vectors that may transmit Lyme disease, Rocky Mountain spotted fever, babesiosis,*

ehrlichiosis, bartonellosis, hepatozoonosis, leishmaniasis, tularemia and heartworm disease".

32. On page 12, delete the claim "*Kills and repels flies that cause stress or leave wounds that can lead to secondary infection*", as this implies heightened safety.

33. On page 12, delete the claim "*Aids in the control of sarcoptic mange*".

34. On page 13, delete the claim "*Results indicate that SVP7 repels and prevents fleas from blood feeding on dogs*", as this implies heightened efficacy.

35. On page 13, change "*Kills the vectors that may transmit Lyme disease, Rocky Mountain spotted fever, babesiosis, ehrlichiosis, bartonellosis, hepatozoonosis, leishmaniasis and heartworm disease*" to read "*Kills the listed vectors that may transmit Lyme disease, Rocky Mountain spotted fever, babesiosis, ehrlichiosis, bartonellosis, hepatozoonosis, leishmaniasis and heartworm disease*".

36. On page 13, change "*Using the (patented) (Trademark) applicator, SVP7 is specifically designed to spread naturally over the dog's body providing effective control of fleas, ticks, biting flies, lice, mites, and mosquitoes for thirty days (four weeks, one month)*" to read "*Using the (patented) (Trademark) applicator, SVP7 is specifically designed to spread naturally over the dog's body providing effective control of fleas, ticks, lice, mites (excluding mange mites), and mosquitoes for thirty days (four weeks, one month)*", as Vectra 3D showed an efficacy of >90% against the biting house fly for only three weeks.

37. On page 13, change "*Repellency against fleas, ticks, mosquitoes, lice, mites, fire ants, and biting flies for 4 weeks (30 days) (one month)*" to read "*Repellency against fleas, ticks, mosquitoes, lice, and mites (excluding mange mites) for 4 weeks (30 days) (one month)*", as Vectra 3D showed an efficacy of >90% against the biting house fly for only three weeks.

38. On page 13, delete the claims "*Significantly reduces flea feeding*" and "*Results indicate that SVP7 repels and prevents fleas from bloodfeeding on dogs*".

39. On page 13, delete "*Reduces flea feeding within 5 minutes*", as this implies heightened efficacy.