Date of Approval: March 13, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-261

WORMXPLUS/VIRBANTEL

pyrantel pamoate/praziquantel
Flavored Chewables
Dogs and puppies

For the treatment and control of roundworms *(Toxocara canis, Toxascaris leonina)*; hookworms *(Ancylostoma caninum, Ancylostoma braziliense, Uncinaria stenocephala*); and tapeworms (*Dipylidium caninum, Taenia pisiformis*) in dogs and puppies.

Sponsored by:

Virbac AH, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-261
B. Sponsor:	Virbac AH, Inc. 3200 Meacham Blvd. Ft. Worth, TX 76137 Drug Labeler Code: 051311
C. Proprietary Name(s):	WORMXPLUS* Flavored Chewables VIRBANTEL Flavored Chewables
D. Established Name(s):	Pyrantel pamoate /Praziquantel
E. Pharmacological Category:	Anthelmintic
F. Dosage Form(s):	Flavored Chewable
G. Amount of Active Ingredient(s):	Small chewable size: 30 mg of pyrantel pamoate and 30 mg of praziquantel. Large chewable size: 114 mg of pyrantel pamoate and 114 mg of praziquantel
H. How Supplied:	WORMXPLUS: Blisters of 2, 4, or 12 chewables. VIRBANTEL: Bottles of 100 or 250 chewables.
I. How Dispensed:	OTC
J. Dosage(s):	A minimum dose of 5 mg pyrantel pamoate and 5 mg praziquantel per kg body weight, (2.27 mg pyrantel pamoate and 2.27 mg praziquantel per lb body weight), according to the following dosing tables.

* Note that WORMXPLUS and VIRBANTEL are identical products. The product is marketed under two trade names. In this FOI Summary, only the WORMXPLUS trade name will be used for simplicity. Any statements regarding WORMXPLUS apply to the VIRBANTEL product as well.

Dog Weight	Number of 30 mg Chewables
6.0 to12.0 pounds	1
12.1 to 25.0 pounds	2
More than 25 pounds	Use the 114 mg size

Dog Weight	Number of 114 mg Chewables
6 to 25 pounds	Use the 30 mg size
25.1 to 50 pounds	1
50.1 to 100 pounds	2
100.1 to 150 pounds	3
150.1 to 200 pounds	4

K. Route(s) of Administration: Oral

L. Species/Class(es): Dogs and puppies

M. Indication(s): For the treatment and control of roundworms *(Toxocara canis, Toxascaris leonina)*; hookworms *(Ancylostoma caninum, Ancylostoma braziliense, Uncinaria stenocephala)*; and tapeworms (*Dipylidium caninum, Taenia pisiformis*) in dogs and puppies.

II. EFFECTIVENESS:

A. Dosage Characterization:

The minimum dose of 5 mg/kg pyrantel pamoate for dogs 6 pounds and greater is supported by data contained in Virbac's approved ANADA 200-281 (pyrantel pamoate) and in ANADA 200-302 (ivermectin/pyrantel pamoate).

The minimum dose of 5 mg/kg praziquantel for dogs weighing 25 pounds or greater is supported by published literature[1,2,3]. The minimum dose of 5 mg/kg praziquantel for smaller dogs is supported by the following dose confirmation study.

D. caninum Dose-confirmation study in dogs weighing less than 15 pounds:

a) Purpose:	Confirm the effectiveness of the two-way combination of pyrantel pamoate and praziquantel for the treatment of tapeworm (*D. caninum*) infection in dogs weighing less than 15 pounds
b) Investigator:	Dawie J. Kok, D.Sc.
c) Study location:	ClinVet International (Pty) Ltd Bloemfontein Republic of South Africa
d) Animals:	5 male and 11 female dogs, of various breeds, weighing 4.63 to 10.58 pounds, naturally infected with *D. caninum*
e) Groups:	Group 1 (n=8): placebo Group 2 (n=8): pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg

1 Georgi JR. Tapeworms. *Veterinary Clinics of North America: Small Animal Practice* 1987;17(6):1285-1305.

2 Dey-Hazra A. The efficacy of DRONCIT (Praziquantel) against Tapeworm Infections in Dog and Cat. *Vet Med Rev* 1976;2:131-141

3 Kruckenberg SM, Meyer AD, Eastman WR. Preliminary studies on the effect of praziquantel against tapeworms in dogs and cats. *Vet Med Small Anim Clin* 1981;76:689-693.

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design:
Day -10: applied flea adulticide to all dogs to prevent re-infection with *D. caninum*
Day -2: allocation to a treatment group
Day 0: treatment
Day 14: necropsy (worm counts)

h) Study results:
Group 1: 8 dogs with *D. caninum* GM= 10.27 (range: 1-164)
Group 2: 0 dogs with *D. caninum* GM= 0
Group 2 vs. Group 1* - Effectiveness: 100%
*statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *D. caninum* infection in dogs weighing less than 15 pounds was demonstrated.

j) Adverse reactions: Three dogs (one from the treated group) had diarrhea before treatment, and two dogs from each group had isolated episodes of diarrhea up to 7 days after treatment.

B. Substantial Evidence:

Treatment and control of roundworms *(Toxocara canis, Toxascaris leonina)* and hookworms *(Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense)*

1. Dose-limiting Ascarid Study 1:

a) Purpose:
i) Demonstrate the non-interference of praziquantel with the effectiveness of pyrantel pamoate to treat and control *T. canis* (dose-limiting parasite)

ii) Confirm the effectiveness of the two-way combination for the treatment of roundworm (*T. canis*) infection in dogs

b) Investigator: John W. McCall, M.S., Ph.D.

c) Study location: TRS LABS Inc.
Athens, GA

d) Animals: 12 male and 12 female parasite naïve Beagle dogs, 8-9 weeks old at the time of inoculation

e) Groups: Group 1 (n=8): placebo
Group 2 (n=8): praziquantel 5 mg/kg
Group 3 (n=8): pyrantel 5 mg/kg and praziquantel 5 mg/kg

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{(\text{control GM} - \text{treated GM})}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design: Day -49: inoculation with 300 embryonated *T. canis* eggs per os
Day 0: allocation to a treatment group and treatment
Day 7: necropsy (worm counts)

h) Study results: Group 1: 8 dogs with *T. canis* GM=18.33 (range: 6-56)
Group 2: 8 dogs with *T. canis* GM=40.99 (range: 19-66)
Group 3: 2 dogs with *T. canis* GM=0.25 (range: 0-2)
Group 3 vs. Group 1* - Effectiveness: 98.6%
Group 3 vs. Group 2* - Effectiveness: 99.4%
*statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *T. canis* infection was demonstrated (> 90%). The non-interference of praziquantel in the combination was demonstrated.

j) Adverse reactions: None reported

2. Dose-limiting Ascarid Study 2:

a) Purpose: i) Demonstrate the non-interference of praziquantel with the effectiveness of pyrantel pamoate to treat and control *T. canis* (dose-limiting parasite)

ii) Confirm the effectiveness of the two-way combination for the treatment of roundworm (*T. canis*) infection in dogs

b) Investigator: John W. McCall, M.S., Ph.D

c) Study location: TRS LABS Inc.
Athens, GA

d) Animals: 18 male and 18 female parasite naïve Beagle dogs, 9 weeks old at the time of inoculation

e) Groups: Group 1 (n=9): placebo
Group 2 (n=9): praziquantel 5 mg/kg
Group 3 (n=9): pyrantel pamoate 5 mg/kg
Group 4 (n=9): pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control groups by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{(\text{control GM} - \text{treated GM})}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design: Day -49: inoculation with 300 embryonated *T. canis* eggs per os
Day 0: allocation to a treatment group and treatment
Day 7: necropsy (worm counts)

h) Study results: Group 1: 9 dogs with *T. canis* GM=18.43, (range: 8-59)
Group 2: 9 dogs with *T. canis* GM=19.61, (range: 3-65)
Group 3: 6 dogs with *T. canis* GM=2.57, (range: 0-11)
Group 4: 5 dogs with *T. canis* GM=1.22, (range: 0-8)
Group 4 vs. Group 1* - Effectiveness: 93%
Group 3 vs. Group 1 *- Effectiveness: 86%
Group 4 vs. Group 2 *- Effectiveness: 94%
Group 4 vs. Group 3**
*statistically significant, α=0.05
**not statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *T. canis* infection was demonstrated (> 90%). The non-interference of praziquantel in the combination was demonstrated.

j) Adverse reactions: None reported

Treatment and control of tapeworms (*Dipylidium caninum, Taenia pisiformis*)

1. <u>*Dipylidium caninum* Non-interference Study:</u>

a) Purpose: i) Demonstrate the non-interference of pyrantel pamoate (in combination with ivermectin) with praziquantel to treat and control *D. caninum*

ii) Confirm the effectiveness of the two-way combination for the treatment of tapeworm (*D. caninum*) infection in dogs

b) Investigator: Dawie J. Kok, D.Sc.

c) Study Location: ClinVet International (Pty) Ltd
Bloemfontein
Republic of South Africa

d) Animals: 9 male and 15 female adult dogs, of various breeds, naturally infected with *D. caninum*

e) Groups: Group 1 (n=8): placebo
Group 2 (n=8): ivermectin 6 mcg/kg and pyrantel

pamoate 5 mg/kg
Group 3 (n=8): pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{(\text{control GM} - \text{treated GM})}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design: Day -1: allocation to a treatment group
Day 0: treatment
Day 14: necropsy (worm counts)

h) Study results: Group 1: 8 dogs with *D. caninum* GM= 6.95 (range: 2-51)
Group 2: 8 dogs with *D. caninum* GM= 23.91 (range: 5-179)
Group 3: 0 dogs with *D. caninum* GM= 0
Group 3 vs. Group 1 *- Effectiveness: 100%
Group 3 vs. Group 2 *- Effectiveness: 100%
*statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *D. caninum* infection and non-interference of pyrantel pamoate was demonstrated.

j) Adverse reactions: None reported

2. *Dipylidium caninum* Dose-confirmation Study:

a) Purpose: Confirm the effectiveness of the two-way combination for the treatment of tapeworm (*D. caninum*) infection in dogs

b) Investigator: Dwight D. Bowman, M.S., Ph.D.

c) Study location: CHK R&D
Stanwood, MI

d) Animals: 7 male and 9 female dogs of various breeds naturally

infected with *D. caninum*

e) Groups: Group 1 (n=8): placebo
Group 2 (n=8): pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design: Day -1: group allocation
Day 0: treatment
Day 14: necropsy (worm counts)

h) Study results: Group 1: 8 dogs with *D. caninum* GM=12.93 (range: 1-134)
Group 2: 0 dogs with *D. caninum* GM=0
Group 1 vs. Group 2*: 100% effectiveness
*statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *D. caninum* was demonstrated.

j) Adverse reactions: None reported

3. *Taenia pisiformis* Dose-confirmation Study:

a) Study Purpose: Confirm the effectiveness of the two-way combination for the treatment of tapeworm (*T. pisiformis*) infection in dogs

b) Investigator: Dwight D. Bowman, M.S., Ph.D.

c) Study location: CHK R&D
Stanwood, MI

d) Animals: 8 male and 8 female dogs of various breeds naturally infected with *T. pisiformis*

e) Groups: Group 1 (n=8): placebo
Group 2 (n=8): pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design: Day -1: group allocation
Day 0: treatment
Day 14: necropsy (worm counts)

h) Study results: Group 1: 7 dogs with *T. pisiformis* GM=3.51 (range: 0-25)
Group 2: 0 dogs with *T. pisiformis* GM=0
Group 1 vs. Group 2*: 100% effectiveness
*statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *T. pisiformis* infection was demonstrated.

j) Adverse reactions: Soft stools on Days 5, 6, 7 and 9 in one dog in the treated group

4. *Taenia pisiformis* Dose-confirmation Study:

a) Study Purpose: Confirm the effectiveness of the two-way combination for the treatment of tapeworm (*T. pisiformis*) infection in dogs

b) Investigator: Allan J. Paul, DVM, M.S.

c) Study location: University of Illinois
Urbana, IL

d) Animals: 10 male and 8 female dogs of various breeds naturally infected with *T. pisiformis*

e) Groups: Group 1 (n=9): placebo

Group 2 (n=9): pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg

f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}} \times 100$$

where GM = geometric mean worm count

g) Study design: Day 0: group allocation
Day 0: treatment
Day 14: necropsy (worm counts)

h) Study results: Group 1: 9 dogs with *T. pisiformis* GM= 4.4 (range: 1-73)
Group 2: 0 dogs with *T. pisiformis* GM=0
Group 1 vs. Group 2*: 100% effectiveness
*statistically significant, α=0.05

i) Conclusion: Effectiveness of the two-way combination against *T. pisiformis* infection was demonstrated.

j) Adverse reactions: None reported

III. TARGET ANIMAL SAFETY:

A. Target Animal Safety (1X, 3X, 5X)

(1) Type of Study: Target animal safety

(2) Study Director: C. Steve Godin, Ph.D., D.A.B.T.
MPI Research, Inc.
Mattawan, Michigan

(3) General Design of the Study:

(a) Good Laboratory Practice Compliance: This study was conducted in compliance with 21 CFR Part 58.

(b) Purpose: To evaluate the safety of WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables in dogs. Safety was assessed after dosing at 1, 3, and 5X multiples of the maximum

potential exposure dose of 11 mg/kg pyrantel pamoate and 11 mg/kg praziquantel based on product labeling.

(c) Test Animals: Thirty-two 12-week-old healthy Beagles, weighing between 2.65 and 4.64 kg at the beginning of the study. Four male and four female puppies were randomly assigned to each treatment group.

(d) Control Drug: The placebo was identical to WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables without the active ingredients.

(e) Dosage Form: Chewable tablets (final market formulation)

(f) Route of Administration: Oral

(g) Dosages: 0, 11 (1X), 33 (3X), and 55 (5X) mg/kg of pyrantel pamoate and praziquantel each once daily for three consecutive days (Days 1, 2, 3) with a four-day non-treatment interval followed by a second three-day treatment period (Days 8, 9, 10). The control group received five placebo chewables at each treatment.

(h) Test Duration: 19 days

(i) Pertinent Variables/Observations: General health observations were made twice daily during the study period for signs of morbidity, mortality, injury, availability of food and water, general health, behavior, and stool character.

Food consumption was measured daily beginning on Day 1 through Day 17. Body weights were measured on Days -1, 7, and 17. Physical examinations were conducted on Days -4, 1, 4, 7, 11, and 16. Post-treatment observations were made on Days 1, 2, 3, 8, 9, and 10. Hematology, clinical chemistry, and urinalysis samples were collected on Days -6, -4, 4, 11, and 16.

Necropsies were performed on all treatment groups on Days 17 and 18. Macroscopic pathology findings and organ weights were recorded for all animals. Histopathology was conducted only on the control group and the 5X treatment group.

(4) Statistical Methods:

For variables measured multiple times, a repeated measures analysis of variance (RMANOVA) was performed using SAS Proc Mixed. The model included the main effects dose group, sex, time, and all two-way and three-way interactions. Single pretest values or the average of pretest values were used as a covariate. Where appropriate, pair wise

comparisons of the 0X group mean with each treatment group mean were made. For organ weights an analysis of variance (ANOVA) was performed using SAS Proc Mixed. The model included dose group, sex, and dose by sex. Where appropriate, pair wise comparisons of the 0X group mean with each treatment group mean were made. For all these analyses, the experimental unit was the individual dog.

(5) Results:

(a) Mortality: All dogs survived to study termination.

(b) Clinical observations:

Vomiting was the most frequent clinical observation in dogs following treatment. The incidence of vomiting increased with dose. The incidence rate dropped as the number of treatments increased in all dosage groups during the first period (Days 1, 2, and 3) but remained approximately constant during the second period (Days 7, 8, and 9). The table below depicts the incidence of vomiting following treatment among all groups.

Table 1: Incidence of vomiting after treatment

Treatment Group mg/kg pyrantel & mg/kg praziquantel	**Number of Dogs Affected (n=8)** Day 1	Day 2	Day 3	Day 8	Day 9	Day 10
0X (placebo)	1	0	0	1	1	0
1X 11mg/kg	2	2	0	1	2	0
3X 33 mg/kg	8	8	3	6	4	5
5X 55 mg/kg	8	7	3	7	8	7

Decreased activity was observed in 7 animals: 1 in the placebo group, 2 in the 1X group, 2 in the 3X group, and 2 in the 5X group. Tremors were observed following treatment in one dog in each of the 3X and 5X groups. All these signs were mild and transient. No medical care was required and treatment was not discontinued.

(c) Hematology:
There were no clinically relevant changes in the hematology variables. All hematology parameters remained within clinically acceptable limits throughout the study across all treatment groups.

(d) Clinical chemistries:

The dose by time effect was statistically significant for alanine aminotransferase (ALT) ($p=0.0163$). Two pertinent differences

involving this interaction were significant: The 5X dose on Day 11 and the 3X dose on Day 16 had significantly higher means than the control group on their respective days. While elevated, these values remained within expected ranges.

One 5X female had an elevated creatine kinase (CK) at pretest 2 of 1867 U/L, which dropped to 441 and 489 on Day 4 and Day 11, respectively. By Day 16, however the figure had risen again to 810 U/L. This dog experienced vomiting in the first 4 hours following treatment administration on all six days of treatment, but developed no other clinical signs of illness. The dog had no vomiting on any of the non-treatment days. Although the CK rose moderately following treatment from Day 11 to Day 16, the value actually declined overall during treatment with the greatest elevation occurring prior to treatment.

(e) Post-mortem observations: There were no treatment-related findings either at necropsy or upon histopathological examination.

(6) Conclusions:

This study demonstrated WORMXPLUS Flavored Chewables are safe when administered to twelve-week-old puppies at 1, 3, and 5 times the highest mg/kg level of each dose range (maximum potential exposure dosage of 11 mg/kg) based on the product label. Vomiting was the most common clinical observation following treatment. The incidence of vomiting increased with dosage but not with number of treatments administered.

B. Palatability study in laboratory dogs:

(1) Type of Study: Laboratory palatability study

(2) Study Investigator: Lori Carter, B.A.
Stillmeadow, Inc.
Sugar Land, Texas

(3) General Design of the Study:

(a) Good Clinical Practice Compliance: This study was conducted in compliance with Good Clinical Practice Guidance.

(b) Purpose: To determine the palatability of WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables when administered to dogs

(c) Test Animals: Thirty healthy dogs (17 males and 13 females) of various breeds, 7 months to 5 years old, weighing 5.7 to 16.8 kg, and

free from conditions that would interfere with chewing or tasting

(d) Control Drug: None

(e) Dosage Form: Chewable tablets (final market formulation).

(f) Route of Administration: Oral

(g) Dosages: Minimum dose of pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg daily for three consecutive days

(h) Test Duration: April 2003 to November 2003

(i) Study Design: Each dog was treated for three consecutive days with the test article. The day prior to the sequence of three days, the dog received a treat. Twenty percent of the dogs (the six lightest dogs) received the broken form of the test article (two or four halves of a small tablet, depending on the dog's body weight).

(j) Pertinent Variables/Observations:

- Palatability: The WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables were offered to the dog in a bowl and then by hand for a maximum total offering time of 5 minutes. A trial was considered successful if the dog swallowed the chewable(s) entirely from the bowl or from the hand within the allowed time of 5 minutes.
- General health: All animals were also observed daily for morbidity, mortality, injury, general health condition and availability of food and water.
- Body weights: Body weights were measured two days before the first administration.
- Post-dosing observations: All dogs were observed at the time of each treatment and hourly afterwards for 4 hours.

(k) Data Analysis:

To obtain the overall average percent, a percent voluntary acceptance and an overall average percent voluntary acceptance were calculated for each dog as follows:

$$\frac{\text{number of trials for which the dog ate the entire dose}}{\text{total number of trials per dogs}} \times 100$$

$$\frac{\text{sum of all the dogs' voluntary acceptance percentages}}{\text{total number of dogs.}} \times 100$$

(l) Results:

The overall average percent voluntary acceptance for the WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables was 47.8%. For five dogs, the test article was offered for less than 5 minutes on one offering day. No adverse reactions were recorded after the dogs were treated with the WORMXPLUS (Pyrantel pamoate/praziquantel) Flavored Chewables.

(m) Conclusions:

Palatability of the WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables when administered on three consecutive days to laboratory dogs showed less than 50% acceptance. Because the laboratory palatability study failed (< 70%), the sponsor conducted a palatability study in client-owned dogs.

C. Palatability and safety study in client-owned dogs:

(1) Type of Study: Field safety and palatability study

(2) Study Investigators: Kent Cooper, DVM
Grand Prairie, Texas

Mary King, DVM
Arlington, Texas

Robert Lorenz, DVM
Arlington, Texas

(3) General Design of the Study:

(a) Good Clinical Practice Compliance: This study was conducted in compliance with Good Clinical Practice Guidance.

(b) Purpose: To determine the palatability and the safety under field conditions of WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables when administered to client-owned dogs.

(c) Test Animals: One hundred twenty six client-owned dogs (70 females and 56 males) of various breeds, 13 weeks to 14 years old, weighing 1.45 to 42 kg, healthy and free from conditions that would interfere with chewing or tasting (like moderate or advanced periodontal disease).

(d) Control Drug: None.

(e) Dosage Form: Chewable tablets (final market formulation)

(f) Route of Administration: Oral

(g) Dosage: Minimal dose of 5 mg pyrantel pamoate and 5 mg praziquantel per kg body weight – one administration on Day 0 or Day 1.

(h) Test Duration: February to November 2004

(i) Pertinent Variables/Observations:

- Palatability (voluntary acceptance of the chewable within 5 minutes): For each dog, the dog's behavior when offering the tablet was recorded by the owner according to two categories: success (chewable taken by the dog from hand/bowl and swallowed) or failure (chewable taken by the dog in the mouth but not swallowed or not taken at all).
- Physical examination and fecal examination: Performed by the Study Investigator on Day 0. It also included a visual examination of the mouth and teeth.
- Body Weights: Measured on Day 0 by the Study Investigator.
- Post-dosing observations: The pet owner was asked to observe his/her dog after treatment and to report any abnormal observation made within the 24 hours after treatment.

(4) Data analysis:

A percent palatability was computed as:

$$\frac{\text{number of dogs that ate the entire dose}}{\text{total number of dogs offered the chewable}} \times 100$$

(5) Results:

(a) Palatability: Of the 126 cases, 8 cases were not interpretable for palatability assessment. Therefore, palatability was evaluated in a total of 118 dogs. The chewable(s) was (were) presented to the dog by hand (18 dogs), by hand and in the bowl (12 dogs), or in the bowl (88 dogs). Thirty-three dogs received a broken form of the small chewable (one or two halves). Eighty-five of 118 trials were a success. The overall palatability of WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables was 72.0%.

(b) Safety: Out of the 123 dogs for which post-dose observations were recorded by the owner, 110 were clinically normal approximately 1

hour and 24 hours after treatment. The owners of six dogs reported abnormal observations 1 hour after dosing: vomiting (1 dog), vomiting and lethargy (1 dog), lethargy (3 dogs), and increased thirst (1 dog). The owners of eight dogs reported abnormal observations 24 hours after dosing: vomiting (2 dogs), diarrhea (2 dogs), vomiting and bloody diarrhea (1 dog), lethargy continuing from the 1 hour post-dose observation (1 dog), coughing (1 dog), dry mouth and increased thirst (1 dog). The dog with vomiting and bloody diarrhea necessitated treatment and recovered.

(6) Conclusions:

WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables, when administered to client-owned dogs of various breeds and ages has an overall palatability of 72%. This product was safe in client-owned dogs when administered under normal conditions of use. Vomiting, diarrhea (with or without blood), and lethargy were the most common adverse reactions.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to WORMXPLUS:

Keep this and all medication out of the reach of children. To obtain product information including a Material Safety Data Sheet (MSDS), call 1-800-338-3659. (Package insert)

In case of ingestion by humans, contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans. (Carton label)

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that WORMXPLUS, when used according to the label, is safe and effective for the treatment and control of roundworms *(Toxocara canis, Toxascaris leonina),* hookworms *(Ancylostoma caninum, Ancylostoma braziliense, Uncinaria stenocephala),* and tapeworms (*Dipylidium caninum, Taenia pisiformis*) in dogs and puppies.

A. Marketing Status:

The drug can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for the safe and effective lay use of WORMXPLUS (pyrantel pamoate/praziquantel) Flavored Chewables.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval because new studies for substantial evidence of effectiveness and target animal safety studies were conducted.

C. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:

WORMXPLUS

- Package Inserts (Small Dogs and Puppies)
  - 2 or 12 Chewable Tablets
  - 4 or 12 Chewable Tablets
- Package Inserts (Medium and Large Dogs)
  - 2 or 12 Chewable Tablets
  - 4 or 12 Chewable Tablets
- Blister Labels (Small Dogs and Puppies)
- Blister Labels (Medium and Large Dogs)
- Carton Labels (Small Dogs and Puppies)
  - 2 Chewable Tablets
  - 4 Chewable Tablets
  - 12 Chewable Tablets
- Carton Labels (Medium and Large Dogs)
  - 2 Chewable Tablets
  - 4 Chewable Tablets
  - 12 Chewable Tablets

VIRBANTEL

- Bottle Label (Small Dogs and Puppies)
  - 100 count
  - 250 count
- Package Insert (Small Dogs and Puppies)
  - 100 count
  - 250 count
- Bottle Label (Medium and Large Dogs)
  - 100 count

250 count

Package Insert (Medium and Large Dogs)

100 count

250 count