

# Efficacy Evaluation of Flavored Combination Parasiticide Tablets in a Laboratory Study for the Removal of Natural *Dipylidium caninum* (tapeworm) Infections in Dogs

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## ABSTRACT

A pivotal blinded laboratory study was designed to evaluate the efficacy of two novel formulations of flavored combination tablets against *Dipylidium caninum* in naturally infected dogs. One formulation was a 3-way combination of the active ingredients praziquantel, milbemycin oxime and lufenuron; the other was a 2-way combination of praziquantel and milbemycin oxime, both administered orally. The study also included a negative control group that received Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> (milbemycin oxime and lufenuron) and a placebo control group that received vehicle placebo tablets.

Each treatment or control group consisted of 10 dogs and the study was conducted in two phases. Dogs were housed in individual pens from Day -14 until necropsy on Day 12. The selection of study animals was based on infection with *D. caninum* as dem-

onstrated by shed proglottids once before and once during the 14-day acclimatization period. Microfilaria tests were conducted on blood samples collected during acclimatization and only heartworm negative dogs were enrolled in the study. Dogs were blocked by weight and randomly assigned to treatment groups. Male and female animals were represented within every treatment group. Dogs in all groups were treated once on Day 0, within approximately 30 minutes of ingesting a full meal, and observed hourly for the first six hours post-treatment, and then again at 8, 10, 12, 18 and 24 hours post-treatment to determine acute tolerance. General health observations were performed daily for the duration of the study. Dogs were euthanized on Day 12 and the intestines were examined for the presence of *D. caninum*.

One dog in the vehicle placebo group was removed from the trial on Day 6 due to ehrlichiosis. Tapeworms were recovered from 18 of 20 control dogs while no tape-

worms were found in any of the dogs that received either the 3-way or 2-way combination tablets, which contained praziquantel. Therefore, the efficacy against naturally acquired *D. caninum* infection was 100% for both the 3-way and the 2-way combination tablets. Clinical abnormalities were confined to self-limiting gastrointestinal signs observed in both treatment and control groups.

## INTRODUCTION

*Dipylidium caninum* is a cyclophyllidean tapeworm found in numerous domestic and wild animals including dogs, cats, coyotes, wolves, foxes and occasionally people. The parasite enjoys worldwide distribution and was described by ancient civilizations.<sup>1</sup> It is commonly acquired by the ingestion of fleas (ex. *Ctenocephalides felis*) and occasionally lice (ex. *Trichodectes canis*) which become infected as larvae after feeding on *D. caninum* eggs in the environment. After the infected insect (intermediate host) reaches the small intestine of the definitive or accidental host, the tapeworm metacestode emerges and attaches to the intestinal lumen. The adult tapeworm remains attached at the site, presumably for years due to its low immunogenicity, and intermittently sheds egg-containing proglottids which are found in the animal (or human) feces or in the perianal area.<sup>2</sup> Dogs and people can only become colonized by ingesting the infected insect, not by ingesting the proglottid.

Despite wide availability of effective ectoparasiticides, which should eliminate exposure to infected fleas, canine infection with *D. caninum* continues to be a persistent problem. True prevalence data is difficult to obtain due to the intermittent nature of proglottid shedding, but in flea endemic areas, infection estimates ranging up to 62% of dogs have been reported, likely due to discontinuous or no use of ectoparasite control products.<sup>3</sup> In general, clinical manifestations in dogs are mild (changes in food consumption, mild weight loss, dull hair coat) or non-existent, however, malnutrition, perianal irritation, intestinal impaction,

colic, and diarrhea are also possible sequelae. Similar signs may be observed in people who become infected. Although minimally pathogenic, the appearance of proglottids on the dog, in the house, or on a child is repulsive to most people and often provides the impetus to eradicate the infection.<sup>4,5</sup> In addition, it is important to eliminate *D. caninum* infections in order to decrease the potential for infection in other animals or people.

Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> (Novartis Animal Health US, Greensboro NC) contain milbemycin oxime and lufenuron. The formulation is approved for the prevention of heartworm disease, for the prevention and control of flea populations, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworm) and *Trichuris vulpis* (whipworm) infections. The 3-way combination tablet contains milbemycin oxime, lufenuron, and praziquantel. The 2-way combination tablet contains milbemycin oxime and praziquantel. Praziquantel was developed over 30 years ago and is still considered the treatment of choice for *D. caninum*, as well as other, tapeworm infections in both animals and people.<sup>6,7</sup> It is highly effective, well-tolerated at the most commonly prescribed dose of 5 mg/kg, and both veterinarians and physicians are familiar with it.<sup>1,8,9,10</sup>

This report describes a blinded dose confirmation laboratory study conducted using dogs that were naturally infected with *D. caninum*. The study was performed to demonstrate the effectiveness of the 2-way and 3-way combination tablets against dipylidiasis. It was conducted in accordance with international standards of good clinical practices (GCPs; Center for Veterinary Medicine, Food and Drug Administration Guidance for Industry 85: Good Clinical Practices [VICH GL9, May 2001]<sup>11</sup> and New Animal Drugs for Investigational Use, U.S. Code of Federal Regulations Title 21 CFR 511<sup>12</sup>) as well as the Center for Veterinary Medicine, Food and Drug Administration Guidance for Industry 111: Effectiveness of Anthelmin-

**Table 1. Study Design**

Pre-treatment body weight range (kg)	Treatment group	Number of dogs (Phase 1 / Phase 2)	Origin of natural infection
5.1 – 21.3	3-way combination tablet	10 (4 / 6)	Republic of South Africa
	2-way combination tablet	10 (4 / 6)	
	Sentinel® Flavor Tabs®	10 (4 / 6)	
	Placebo	10 (4* / 6)	

\*Only 3 dogs in the Placebo group from Phase 1 were analyzed. One dog (18 8BT) was diagnosed with acute ehrlichiosis and euthanized on Day 6.

tics: Specific Recommendations for Canine [VICH GL19, May 2001]<sup>13</sup> and the recommendations of the World Association for the Advancement of Veterinary Parasitology.<sup>14</sup>

## MATERIALS AND METHODS

### Study design

The efficacies of two novel parasiticide formulations which contain praziquantel were evaluated in a monocentric, blinded and controlled laboratory study that was conducted between August and October 2002 at ClinVet International (Pty.) Ltd., Bloemfontein, South Africa. The study was conducted in two phases to allow recruitment of a sufficient number of dogs with naturally acquired *D. caninum* infections. Details are provided in Table 1, Study Design.

### Study animals

Forty (40) adult dogs of various crossbreeds (15 males and 25 females) naturally infected with *D. caninum*, were used in the study. Dogs were obtained according to standard procedures for the facility and in observance of local regulations. Dogs were identified by either numbered collar tags or implanted transponders.

During the first week of acclimatization, all dogs were inoculated with modified live Canine Distemper-Adenovirus Type 2-Parainfluenza-Parvovirus vaccine, received a dose of imidocarb (Forray® 65; MSD Animal Health, South Africa) to eliminate occult hematoprotzoan infections,

and were dipped in flumethrin (Bayticol®; Bayer Healthcare, South Africa) to remove ectoparasites. No topical or systemic anthelmintic treatments were administered before or during the study.

Dogs were selected for inclusion in the study on the basis of infection with *D. caninum*. The presence of *D. caninum* proglottids, recovered by sieving feces, was confirmed for all dogs within sixteen days prior to receiving the designated treatment. The inclusion of eggs in uterine capsules served as the diagnostic feature for *D. caninum*. All dogs included in the study were diagnosed as infected once before and once during the acclimatization period. After confirmation of infection with *D. caninum*, dogs were kept indoors in individual pens throughout the study until euthanized. Dogs were physiologically mature and healthy (except for the presence of *D. caninum* or other gastrointestinal parasites) as certified by physical examination prior to treatment administration. None of the dogs were pregnant or lactating. Body weight, for dose calculation, was obtained 1 to 2 days prior to treatment using calibrated scales. Dogs enrolled in the study weighed between 5.1 and 21.3 kg prior to treatment and tested negative for heartworm infection as determined by a membrane filtration microfilaria test carried out at the University of Pretoria, Faculty of Veterinary Medicine during the acclimatization period.

**Table 2.** Schedule of Key Study Events

Study Day*	Procedure
-16 to -14	Physical examinations. Onset of acclimatization for animals identified as positive for <i>D. caninum</i> by sieving and microscopic evaluation of feces.
-14 to -7	Dogs dipped in flumethrin (Bayticol®) and received Canine Distemper-Adenovirus Type 2 – Parainfluenza – Parvovirus vaccine and imidocarb (Forray® 65).
-14 to -1	Infection with <i>D. caninum</i> confirmed. Blood samples collected and dogs tested for heartworm infection with a microfilaria test.
-14 to 12	Dogs observed daily for general health.
-2 to -1	Body weight determined before morning feeding. Physical examinations.
-1	Food removed for overnight fasting.
-1 to 0	Dogs assigned to study groups.
0	Dogs treated within 30 minutes of ingesting a full meal.
0 to 1	Dogs observed hourly for the first six hours after treatment, then at 8, 10, 12, 18 and 24 hours.
11	Food removed for overnight fasting.
12	Euthanasia, necropsy and recovery of gastrointestinal tract. Animal phase completed.
≥ 12	Worms recovered at necropsy, identified and counted.

\*Both phases of the study were conducted according to the same study schedule

The study protocol was approved by the ClinVet Animal Ethics Committee (CAEC), which is an independent body with members representing specific categories of public interest. The categories are specified in the “National Code for Animal Use in Research, Education, Diagnosis and Testing of Drugs and Related Substances in South Africa.”<sup>15</sup> Furthermore, the dogs were housed in compliance with the National Code. The studies were performed in compliance with institutional, governmental or international guidelines for research on animals.

Details related to the various study events are described in Table 2, Schedule of Key Study Events.

### Treatment

Dogs were blocked by weight and assigned to treatment groups using SAS generated (SAS Stat®, SAS Institute, Inc., Cary NC) forms provided by the Sponsor. Since the various treatments and controls differed in appearance, blinding was accomplished by separation of function. An unblinded dispenser was selected for each phase to ensure that blinding was maintained. The dispensers’ function was to dispense and administer all treatments. Individuals who were responsible for the collection and interpretation of efficacy and safety data were blinded to treatment allocation throughout the duration of the study. The dispenser

did not participate in critical end point data gathering or interpretation.

Dose bands were equivalent to approved Sentinel® Flavor Tabs® dose bands and based on body weight. All dogs received the appropriate sized tablet. Animals were treated once only, on Day 0, with orally administered investigational tablets or control tablets within 30 minutes of ingesting a full meal following an overnight fast. Whole tablets were administered by the designated, unblinded dispenser who ensured that all tablets were swallowed completely. No dogs vomited within one hour of drug administration, therefore, no dogs were redosed. Details are presented in Table 3, Dosing Chart.

Dosing within 30 minutes of consuming a meal, after an overnight fast, is not required for absorption of praziquantel or

milbemycin oxime, but food is essential for adequate absorption of lufenuron. Sentinel® Flavor Tabs® and the 3-way combination tablet both contain lufenuron. The label directions for Sentinel® Flavor Tabs® indicate this particular regimen for dosing, therefore, to maintain blinding, all treatment and control products were administered after fasting and within 30 minutes of eating. There is no detrimental effect on the absorption of the 2-way formulation when administered in this manner.

### Health observations

Observations to determine the general health condition of the dogs were performed once daily from Day -14 through Day 12, except on the day of treatment (Day 0). Day 0 observations were conducted every hour for six hours post-dosing; then at 8, 10, 12, 18, and 24 hours post-dosing. The Day 0 obser-

**Table 3. Dosing Chart**

Treatment group	Tablet composition (P=praziquantel, MO=milbemycin oxime, L=lufenuron)	Body weight*	Number of tablets administered	Number of dogs
3-way combination tablets	P – 57 mg MO – 5.75 mg L – 115 mg	11 – 25 lbs (5.0 – 11.4 kg)	One	10 (4 + 6)**
	P – 114 mg MO – 11.5 mg L – 230 mg	26 – 50 lbs (11.8 – 22.7 kg)	One	
2-way combination tablets	P – 57 mg MO – 5.75 mg	11 – 25 lbs (5.0 – 11.4 kg)	One	10 (4 + 6)
	P – 114 mg MO – 11.5 mg	26 – 50 lbs (11.8 – 22.7 kg)	One	
Sentinel® Flavor Tabs®	MO – 5.75 mg L – 115 mg	11 – 25 lbs (5.0 – 11.4 kg)	One	10 (4 + 6)
	MO – 11.5 mg L – 230 mg	26 – 50 lb (11.8 – 22.7 kg)	One	
Placebo	NA	11 – 25 lbs (5.0 – 11.4 kg)	One	10 (4 + 6)
	NA	26 – 50 lbs (11.8 – 22.7 kg)	One	

\* Dogs weighing in excess of the maximum dose in the weight range received the next highest dose.

\*\* In Phase 1 and 2, respectively.

vations included assessment for vomiting, excessive salivation, diarrhea or any signs of abnormal behavior. Health observations were performed by veterinarians or staff who were blinded to treatment groups.

### Assessment of Efficacy

All dogs were euthanized (Euthapent<sup>®</sup>, Kyron Laboratories, South Africa) and necropsied for *D. caninum* recovery and enumeration on Day 12. Food was withheld overnight from all animals before termination in order to minimize intestinal contents at the time of euthanasia. The digestive tract from stomach to rectum of each dog was removed. A longitudinal incision was made, the tract was opened and the intestinal contents plus the yield of several mucosal strippings were washed through sieves of decreasing mesh size. Care was taken to recover all worms attached to the intestinal wall. All of the sieves were back-washed and samples were examined under a stereomicroscope in order to count all *D. caninum* scoleces. *D. caninum* segments or worm fragments and other intestinal parasites were not counted.

### Assessment of safety

Safety was evaluated by clinical observation and all adverse events were recorded. None of the dogs received treatment for an adverse event during the study.

### STATISTICAL ANALYSIS

The dog was the experimental unit in this study. All hypotheses were tested at a 2-sided 0.05 level of significance.

The outcome variable used for the determination of efficacy was the number of *D. caninum* scoleces (since praziquantel causes fragmentation and disintegration of the tapeworm) recovered during post-mortem examination on Day 12. One dog was removed from the study on Day 6, diagnosed with ehrlichiosis and not used in the statistical analysis. A minimum of six dogs, each harboring a minimum of 5 worms, were required in both the positive control and placebo control groups to provide evidence of substantial infection for the study to be

considered valid.<sup>13</sup>

Efficacy was determined on the basis of the percent reduction in tapeworm counts in the 3-way and 2-way treated groups compared to the Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> and control groups. Geometric means of tapeworm counts were calculated and efficacy was determined as follows:

$$\text{Percent Efficacy} = 100 \times (\text{cc} - \text{ct}) / \text{cc}$$

Where: cc = geometric mean number of parasites in the placebo group

ct = geometric mean number of parasites in the treatment group

There were separate calculations for the 3-way combination tablets, 2-way combination tablets and Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup>. A treatment was considered efficacious if percent efficacy was  $\geq 90\%$ . All analyses were performed using SAS/STAT<sup>®</sup> software (Version 8 of the SAS System for Windows, Copyright<sup>®</sup> 2004 by SAS Institute Inc., Cary, NC, USA).

A mixed model analysis of variance was performed on the log-transformed worm counts obtained from every dog at necropsy using SAS/STAT<sup>®</sup> (SAS Institute, Inc., Cary, NC) to test the sufficiency of the model and to test the following hypotheses:

a)  $H_0$ : 3-way worm counts  $\geq$  Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> worm counts, versus

$H_a$ : 3-way worm counts  $<$  Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> worm counts, and

b)  $H_0$ : 3-way worm counts  $\geq$  Placebo worm counts, versus

$H_a$ : 3-way worm counts  $<$  Placebo worm counts, and

c)  $H_0$ : 2-way worm counts  $\geq$  Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> worm counts, versus

$H_a$ : 2-way worm counts  $<$  Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> worm counts, and

d)  $H_0$ : 2-way worm counts  $\geq$  Placebo worm counts, versus

$H_a$ : 2-way worm counts  $<$  Placebo worm counts

Classification variables used in the ANOVA included treatment, sex, phase, and the interaction treatment by sex.

**Table 4.** Summary Statistics and Percent Effectiveness

Treatment group	N	Mean tapeworm counts*	Standard deviation	Geometric mean tapeworm counts*	Percent effectiveness <sup>^</sup>
3-way combination tablets	10	0.00	0.00	0.00	100%
2-way combination tablets	10	0.00	0.00	0.00	100%
Sentinel <sup>®</sup> Flavor Tabs <sup>®</sup>	10	23.90	33.17	9.98	26.7%
Placebo	9	61.33	103.61	13.60 <sup>†</sup>	NA

\* Counts are based on the number of scoleces, not fragments, recovered

<sup>^</sup> Percent effectiveness is based on comparison to the Placebo

<sup>†</sup> Dog diagnosed with ehrlichiosis is not included in data set

NA = Not Applicable

## RESULTS

### Efficacy

Of the 40 dogs that were enrolled in the study, only one dog, which was diagnosed with ehrlichiosis on Day 6 and subsequently euthanized, was not included in the final analysis for effectiveness.

The arithmetic and geometric mean numbers of *D. caninum* recovered at necropsy, and percent effectiveness are presented in Table 4, Summary Statistics and Percent Effectiveness. Five or more scoleces were found in six dogs in the placebo-treated control group, thereby validating the infection level in study dogs.

Both the 2-way and 3-way combination tablets administered at 5 mg/kg praziquantel

were 100% effective and completely eliminated all *D. caninum* in the small intestine of treated dogs. Statistically significant differences were observed in worm counts between dogs that received either the 2-way or 3-way combination tablet and dogs that did not as shown in Table 5, Mixed Model ANOVA - Results. There was no statistically significant difference observed between the Sentinel<sup>®</sup> Flavor Tabs<sup>®</sup> and Placebo-dosed groups.

Because the statistical comparison of these results led to in the rejection of the null hypothesis and because the percent efficacy for each combination formulation was 100%, both test articles were judged effective for the removal of natural *D. caninum*

**Table 5.** Mixed Model ANOVA - Results

Treatment contrast	vs. Treatment group	p-value*
3-way combination	Placebo	0.0001
	Sentinel <sup>®</sup> Flavor Tabs <sup>®</sup>	0.0001
2-way combination	Placebo	0.0002
	Sentinel <sup>®</sup> Flavor Tabs <sup>®</sup>	0.0002
Sentinel <sup>®</sup> Flavor Tabs <sup>®</sup>	Placebo	0.8186

\* Results from ANOVA tested at 2-sided 5% level of significance

**Table 6.** *Gastrointestinal Events\**

Treatment group	Frequency of event / number of animals affected	Number of affected dogs/dogs in group (percent affected)
3-way combination tablets	6 / 4	4/10 (40%)
2-way combination tablets	11 / 5	5/10 (50%)
Sentinel® Flavor Tabs®	6 / 4	4/10 (40%)
Placebo	3 / 2	2/9** (20%)

\* *Soft/loose/liquid/watery feces (diarrhea)*

\*\* *One dog diagnosed with ehrlichiosis on Day 6 is not included in data set*

(tapeworm) infections in dogs.

### Safety

Clinical findings are summarized in Table 6, Gastrointestinal Events, which presents the number of animals and frequency of events during the study. No conditions other than those shown in the table were observed during daily health observations or post-dose observations by the Study Veterinarian or other trained staff members. Abnormalities were limited to clinical signs consisting primarily of various degrees of soft or loose feces (ranging from soft formed to fluid or diarrhetic feces) sometimes with blood present. Tapeworm fragments were often expelled in the feces at the same time. Clinical abnormalities were intermittently reported across all treatment groups throughout the study period. None of the conditions persisted and most incidences were mild, therefore, no concomitant treatments were administered to any dog. Because there was no clear pattern of occurrence of these adverse events it is considered unlikely that there was a causal relationship between any of the cases of soft/loose feces or diarrhea and the administration of investigational/control products. The presence of other parasitic worms (as these were naturally infected dogs), the killing of worms following treatment, the handling of animals during the study or other external conditions could have precipitated the abnormalities.

The single administration of both combination test articles was well tolerated; no clinical signs related to administration of the

test article were observed during the study.

### DISCUSSION

The reported prevalence of tapeworms in dogs ranges from 2.0% to approximately 60.0%.<sup>4,16</sup> A number of factors influence the likelihood that a dog or cat will be infected with tapeworms, including the geographic region, age and health condition of the animal, and the opportunity the animal may have to ingest an infected intermediate host (*Ctenocephalides felis*). The gold standard for diagnosing dipylidiasis is post-mortem examination of the intestinal tract. Obviously, this method is not acceptable for determining the prevalence in client-owned animals, so prevalence data is typically generated by fecal flotation or direct observation of proglottids. These methods may substantially underestimate the frequency of infection with cyclophyllidean cestodes because proglottids (and eggs) are focally distributed in fecal material; a given fecal sample may be negative for tapeworm proglottids or eggs, even in the presence of a heavy worm burden.

Intermittent use of flea control products can result in sporadic exposure to fleas which can lead to dipylidiasis in dogs not harboring fleas at the time of diagnosis. Since the prepatent period for *D. caninum* is 2 to 3 weeks, it is imperative that flea populations are eliminated when anthelmintic therapy is instituted. Aside from a single treatment with Bayticol® prior to acclimatization, there was no subsequent effort to eliminate adult fleas on any dogs after

enrollment in the study because the duration of the study was 12 days.

There is no validated model for dipylidiasis, therefore, the antiparasitic activity of the two combination tablet formulations was tested in a population of naturally infected dogs in South Africa. Each formulation contained praziquantel and milbemyacin oxime, while one formulation also contained lufenuron. The veterinary profession is familiar with the cestocidal activity of praziquantel, however, this study further demonstrates 100% effectiveness against *D. caninum* by praziquantel in the presence of milbemyacin oxime or milbemyacin and lufenuron. It was not surprising that worm counts derived from the Sentinel® Flavor Tabs® treated group at necropsy were not significantly different from the placebo treated control since neither of the two control groups received praziquantel.

To date, *D. caninum* resistance to praziquantel has not been reported despite decades of clinical use. Because dogs are treated individually, and praziquantel is 100% effective at the standard dose of 5 mg/kg, it is unlikely that there will be tapeworms surviving to pass along resistance if dogs are treated until cured of the infection.

During the post-treatment observation period, soft/loose feces and diarrhea were intermittently observed. However, various degrees of soft feces, loose feces, or diarrhea are associated with intestinal tapeworm infection and during elimination of dead worms. There was one unanticipated death which occurred when a dog that received the vehicle placebo was removed from the study due to ehrlichiosis and subsequently euthanized for humane reasons. The development of ehrlichiosis was not related to administration of the placebo or the condition of dipylidiasis.

The results of this study confirmed the safety and 100% effectiveness of a 2-way (praziquantel and milbemyacin oxime) and a 3-way (praziquantel, milbemyacin oxime and lufenuron) combination tablet for the removal of natural *D. caninum* (tapeworm)

infections in dogs.

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## REFERENCES

1. Boreham RE, Boreham PFL: *Dipylidium caninum*: Life Cycle, Epizootiology, and Control. *Compend Contin Educ Pract Vet*. 1990; 12:667-675.
2. Parasites and Health. *Dipylidium caninum* infection. Available at <http://www.dpd.cdc.gov/dpdx/HTML/Dipylidium.htm>. Accessed on 06 November 2012.
3. Conboy G: Cestodes of dogs and cats in North America. *Vet Clin North Am Small Anim Pract*. 2009; 39(6):1075-1090.
4. The Companion Animal Parasite Counsel. Current Advice on Parasite Control: Intestinal Parasites: Cyclophylloidean Tapeworm. Available online at <http://www.capcvet.org/capc-recommendations/cyclophylloidean-tapeworm/>. Accessed on 06 November 2012.
5. Weisse ME, Mullins JK, Moffett KS: A Neonate with Worms. *Clin Infect Dis*. 2008; 46:1786-1788.
6. Andrews P, Thomas H, Pohlke R, Seubert J: Praziquantel. *Med Res Rev*. 1983; 3:147-200.
7. Kruckenbergs SM, Meyer AD, Eastman WR: Preliminary studies on the effect of praziquantel against tapeworms in dogs and cats. *Vet Med Small Anim Clin*. 1981; May: 689-693.
8. DD Bowman: Helminths: Treatment of Adult Tapeworm Infections. In: Bowman DD, ed. *Georgis' Parasitology for Veterinarians*, Ninth Edition, St. Louis: Saunders Elsevier; 2009;151.
9. In: Kahn CM, (Ed.): *The Merck Veterinary Manual*, Tenth Edition, Merck and Co, Inc. Whitehouse Station, NJ, 2010;392-393 and 2262.
10. Plumb DC: Praziquantel. In: Plumb DC, ed. *Plumb's Veterinary Drug Handbook*, Fifth Edition, Ames IA: Blackwell Publishing, 2005: 932-935.
11. US FDA Guidance for Industry 85/VICH Topic GL9, Good Clinical Practices (2001, rev. 2011). Available online at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052417.pdf>. Accessed 12 December 2012.
12. US FDA Code of Federal Regulations Title 21 Part 511 New Animal Drugs for Investigational Use (2011). Available online at <http://www.accessdata>.

- fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=511&showFR=1. Accessed 12 December 2012.
13. US FDA Guidance for Industry 111/VICH Topic GL19, Effectiveness of Anthelmintics: Specific Recommendations for Canine (2002). Available online at <http://www.fda.gov/downloads/Animal-Veterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052652.pdf>. Accessed 12 December 2012.
  14. Jacobs DE, Arakawa A, Courtney CH, Gemmell MA, McCall JW, Myers GH, Vanparijs O: World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) guidelines for evaluating the efficacy of anthelmintics for dogs and cats. *Vet Parasitol.* 1994; 52:179-202.
  15. National Code for Animal Use in Research, Education, Diagnosis and Testing of Drugs and Related Substances in South Africa (Director General of Agriculture, Pretoria South Africa).
  16. Tupler R, Levy JK, Sabshin SJ, Tucker SJ, Greiner EC, Leutenegger CM: Enteropathogens identified in dogs entering a Florida animal shelter with normal feces or diarrhea. *J Am Vet Med Assoc.* 2012; 241:338-343.