Approval Date: May 19, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-007

B. Sponsor

Miles, Inc.
Agriculture Division
Animal Health Products
P. O. Box 390
Shawnee Mission, Kansas 66201

C. Proprietary Name

Drontal™ Plus Broad Spectrum Anthelmintic Tablets

D. Established Name

Praziquantel + Pyrantel Pamoate + Febantel

E. Dispensing Status

Rx

F. Dosage Form, Dosage Regimen, and Route of Administration

Drontal™ Plus Broad Spectrum Anthelmintic Tablets are available in two sizes to be administered as a single dosage (directly by mouth or offered in the food) as appropriate for the weight of the dog.

For small dogs* (up to 25 lbs) - tablets containing 22.7 mg praziquantel, 22.7 mg pyrantel base and 113.4 mg febantel/scored tablet.

Body Weight (Lb.)	Number of Tablets
2 - 4	0.5
5 - 7	1.0
8 - 12	1.5
13-18	2.0
19-25	2.5

*NOT FOR USE IN DOGS WEIGHING LESS THAN 2 LBS. OR PUPPIES LESS THAN 3 WEEKS OF AGE.

For medium and large dogs (26 lbs and over) - tablets containing 68.0 mg praziquantel, 68.09 mg pyrantel base and 340.2 mg febantel/scored tablet.

Body Weight (Lb.)	Number of Tablets
26-30	1.0
31-44	1.5
45-60	2.0
61-74	2.5
75-90	3.0
91-104	3.5
105-120	4.0

The tablet formulations and dosage tables were designed to provide the current approved dosage (5-10 mg/kg) of praziquantel (Droncit®; MOBAY NADA No. 111-798) for 100% elimination of tapeworms; 5 - 10 mg/kg (2.27 - 4.54 mg/lb) pyrantel base for dogs under 5 lbs for removal of hookworms and ascarids; and at least 25 mg/kg (11.35 mg/lb) febantel for removal of whipworms.

G. Indication

Drontal™ Plus Broad Spectrum Anthelmintic Tablets are indicated for the removal of the following intestinal parasites in dogs:

- Tapeworms (*Dipylidium caninum, Taenia pisiformis, Echinococcus granulosus*)
- Hookworms (*Ancylostoma caninum, Incinaria stenocephala*)
- Ascarids (*Toxocara canis, Toxascaris leonina*)
- Whipworms (*Trichuris vulpis*)

II. EFFECTIVENESS

In the following discussion, laboratory and/or clinical field studies were conducted to demonstrate efficacy against each parasite species claimed in the labeling, except *Echinococcus granulosus*. It was not necessary for the sponsor to conduct any additional studies for this parasite, since definitive diagnosis is very difficult and natural infections are rare. Please refer to the Freedom of Information summary for NADA 111-798, in which the sponsor previously demonstrated effectiveness against *Echinococcus granulosus* in dogs experimentally infected in a laboratory study.

A. Pivotal Well-Controlled Laboratory Efficacy Studies.

Four adequate and well-controlled laboratory efficacy studies utilizing 176 dogs infected with various parasite species were pivotal in demonstrating the efficacy of Drontal Plus Tablets for removal of the parasites indicated on the label. Parasite infections were diagnosed by fecal examinations prior to including dogs in each study.

The following tablet formulations were included in the four controlled efficacy laboratory studies.

Formulation and Dosage	**Evaluated in Laboratory Study Numbers**
Pyrantel Tablets: 5 mg/kg (2.27 mg/lb)	1,2,3
Praziquantel + Pyrantel Tablets: mg/kg (2.27 mg/lb) of each active	1,2,3,4,5
Drontal Plus Tablets: 5 mg/kg (2.27 mg/lb) of praziquantel and pyrantel base + 25 mg/kg (11.35 mg/lb) febantel (The formulation to be marketed)	1,2,3,4
Febantel Tablets: 25 mg/kg (11.35 mg/lb)	4
Placebo Tablets	1,2,3,4

Data regarding the efficacy of the tablets for removal of whipworms (*Trichuris vulpis*) from Laboratory Study Nos. 1 and 4 were combined for statistical analysis as a separate report.

These studies were conducted in accordance with the FDA Canine/Feline Anthelmintic Guidelines. Each dog was treated with the designated tablet formulation. Control dogs in each study were treated with placebo (blank) tablets. The studies were blinded in that the investigators were not aware of the content of the tablet formulations until the studies were concluded. Seven days after treatment the dogs were euthanatized and the gastrointestinal tract was removed and examined for all remaining parasites. Percent efficacy was calculated for each parasite species from the number of parasites recovered at necropsy using the following formula:

$$\frac{Mean\ No.of\ Parasites\ in\ Control\ Animals - Mean\ No.of\ Parasites\ in\ the\ Treated\ Animals}{Mean\ No.\ of\ Parasites\ in\ the\ Control\ Animals} x\ 100 = \%\ Efficacy$$

Worm recovery data were analyzed statistically using nonparametric methodology.

The studies demonstrated the following: (1) neither pyrantel nor febantel interfere with the activity of praziquantel against tapeworms, (2) neither praziquantel nor febantel interfere with the activity of pyrantel against hookworms or ascarids, (3) the combination of pyrantel with febantel provides effective removal of whipworms.

1. Laboratory Study No. 1: Dr. D. Bowman, Stanwood, Michigan

A total of 48 mixed-breed dogs (25 males and 23 females) with naturally acquired infections of *Ancylostoma caninum* and *Toxocara canis* were included in the study. Twenty-five of the dogs were also infected with *Trichuris vulpis*. The 48 dogs were randomized into 4 groups (of 12 dogs each). Each group was treated with pyrantel tablets, praziquantel + pyrantel tablets, Drontal Plus Tablets or placebo tablets (control). No side effects were observed after treatment. Treatments, recovery of parasites at necropsy, and efficacy information are given in Table 1.

Table 1. Summary of Efficacy: Laboratory Study No.1

Treatment	Controlled Percent Efficacy (No. of Dogs Infected) *Ancylostoma caninum*	Controlled Percent Efficacy (No. of Dogs Infected) *Toxocara canis*	Controlled Percent Efficacy (No. of Dogs Infected) *Trichuris* vulpis*
Pyrantel Tablets	99.48 (10)	95.40 (10)	0.00 (7)
Praziquantel + Pyrantel Tablets	99.83 (10)	95.97 (10)	0.00 (6)
Praziquantel + pyrantel + febantel	100 (10)	99.68 (9)	93.99 (5)
[Control: X Worms/Dog]	[57.90] (11)	[34.77] (9)	[59.86] (7)

*Efficacy data for removal of *T. vulpis* from this study and Lab. Study No. 4 were combined for statistical analysis. See Table 5.

Conclusions: There were no significant differences between the 3 tablet formulations for removal of *A. caninum* or *T. canis* ($P > 0.0688$). The results of the study demonstrated the efficacy of pyrantel tablets alone for the removal of hookworms (*A. caninum*) and ascarids (*T. canis*). Praziquantel did not interfere with the activity of pyrantel for removal of either parasite. Pyrantel tablets alone and praziquantel + pyrantel tablets were not efficacious for the removal of whipworms (*T. vulpis*). Drontal Plus (praziquantel + pyrantel + febantel) Tablets were efficacious for the removal of *A. caninum*, *T. canis* and *T. vulpis*.

2. Laboratory Study No. 2: Dr. L. Cruthers, Corapeake, N.C.

A total of 40 mixed-breed dogs (26 males and 14 females) with naturally acquired infections of *Ancylostoma caninum* and *Incinaria stenocephala* were included in the study. The 40 dogs were randomized into 4 groups (of 10 dogs each). Each group was treated with pyrantel tablets, praziquantel + pyrantel tablets, Drontal Plus Tablets or placebo tablets (control). No side effects were observed after treatment. Treatments, recovery of parasites at necropsy and efficacy information are given in Table 2.

Table 2. Summary of Efficacy: Laboratory Study No. 2

Treatment	Controlled Percent Efficacy (No. of Dogs Infected) *Ancylostoma caninum*	Controlled Percent Efficacy (No. of Dogs Infected) *Uncinaria stenocephala*
Pyrantel Tablets	96.0 (7)	85.3 (10)
Praziquantel + Pyrantel Tablets	80.0 (8)	74.0 (10)
Praziquantel + pyrantel + febantel	99.6 (9)	99.8 (9)
[Control: X Worms/Dog]	[124.0] (8)	[123.4] (10)

Conclusions: The results of the study demonstrated the efficacy of pyrantel tablets alone for the removal of both hookworm species. The efficacy of praziquantel + pyrantel tablets for both species was less than that observed with pyrantel tablets although the difference was not statistically significant (P greater than or equal to 0.3110). The combined nematocidal activity of febantel with pyrantel in Drontal Plus Tablets resulted in a significant increase in the efficacy of removal of both hookworm species (P less than or equal to 0.0483). Drontal Plus (praziquantel + pyrantel + febantel) Tablets were efficacious for the removal of *A. caninum* and *I. stenocephala*.

3. Laboratory Study No. 3: Dr. L. Cruthers, Corapeake, N.C.

A total of 48 beagles (20 males and 28 females) were given 275 embryonated *Toxascaris leonina* eggs to establish infections experimentally. Fifteen weeks later (i.e. when the parasites were mature) the dogs were randomized into 4 groups (of 12 dogs each). Each group was treated with pyrantel tablets, praziquantel + pyrantel tablets, Drontal Plus Tablets or placebo tablets (control). No side effects were observed after treatment. Treatments, recovery of parasites at necropsy, and efficacy information are given in Table 3.

Treatment	Controlled Percent Efficacy (No. of Dogs Infected) *Toxascaris leonina*
Pyrantel Tablets	95.74 (12)
Praziquantel+ Pyrantel Tablets	92.52 (12)
Praziquantel +pyrantel + febantel	97.81 (12)
[Control: X Worms/Dog]	[7.75] (11)

Conclusions: No significant differences were detected among the 3 treated groups for removal of *T. leonina* (P greater than or equal to 0.1673). The results of the study demonstrated pyrantel (alone), praziquantel + pyrantel and Drontal Plus Tablets were efficacious for removal of *T. leonina*. Neither the presence of praziquantel nor febantel interfered with the nematocidal activity of pyrantel.

4. Laboratory Study No. 4: Dr. D. Bowman, Stanwwod, Michigan

A total of 40 mixed-breed dogs (25 males and 15 females) were included in the study. All of the dogs were naturally infected with *Taenia pisiformis*. Many of the dogs were also infected with *Trichuris vulpis*, *Toxocara canis* and *Ancylostoma caninum*. The dogs were randomized into 4 groups (of 10 dogs each). Each group was treated with febantel tablets, praziquantel + pyrantel tablets, Frontal Plus Tablets or placebo tablets (control). No side effects were observed after treatment. Treatments, recovery of parasites at necropsy and efficacy information are given in Table 4.

Table 4 Summary of Efficacy: Laboratory Study No. 4

Treatment	Controlled Percent Efficacy (No. of Dogs Infected) *Taenia pisiformis*	Controlled Percent Efficacy (No. of Dogs Infected) *Trichuris* vulpis*	Controlled Percent Efficacy (No. of Dogs Infected) *Toxocara canis*	Controlled Percent Efficacy (No. of Dogs Infected) *Ancylostoma caninum*
Pyrantel Tablets	97.66 (10)	42.30 (7)	15.07 (3)	84.50 (3)
Praziquantel+ Pyrantel Tablets	100 (10)	0.00 (7)	100 (3)	100 (3)
Praziquantel +pyrantel + febantel	100 (10)	91.31 (7)	92.99 (3)	98.41 (6)
[Control: X Worms/Dog]	[12.80] (10)	[13.12] (8)	[4.71] (7)	[10.71] (7)

*Efficacy data for removal of T. vulpis from this study and Lab. Study No. 1 were combined for statistical analysis. See Table No. 5.

Conclusions: No significant differences were observed among the treated groups for removal of *T. pisiformis* (P greater than or equal to 0.0631). The results of this study demonstrated that praziquantel + pyrantel and Drontal Plus Tablets are effective against *T. pisiformis*. Neither febantel nor pyrantel interfered with the efficacy of praziquantel for removal of tapeworms. These two formulations were also effective for removal of *T. canis* and *A. caninum*.

Praziquantel + pyrantel tablets were not effective for removal of *T. vulpis*. Febantel tablets alone provided reduction of *T. vulpis*. The combined nematocidal activity of pyrantel + febantel in Drontal Plus Tablets provided 91.31% removal *T. vulpis*.

5. Statistical Evaluation of Laboratory Study Nos. 1 and 4.

Data pertaining to the efficacy of praziquantel + pyrantel and Drontal Plus tablets for removal of *T. vulpis* infections in dogs from Laboratory Studies No. 1 and 4 were combined for statistical analysis. The two studies were conducted by the same investigator at the same location using similar protocols. Forty dogs were naturally infected with *T. vulpis* in the two studies. Twelve dogs were treated with Drontal Plus (praziquantel + pyrantel pamoate + febantel) Tablets. Thirteen dogs were treated with praziquantel + pyrantel tablets. Fifteen additional dogs received placebo tablets (controls). The dogs were euthanatized 7 days after treatment and examined for remaining *T. vulpis*. The results are summarized in Table 5.

Table 5. Summary of Laboratory Efficacy Studies with *Trichuris vulpis*

Treatment	Controlled Percent Efficacy (No. of Dogs Infected)
Praziquantel+ Pyrantel Tablets	0.00 (13)
Praziquantel +pyrantel + febantel	94.0 (12)
[Control: X Worms/Dog]	[40.0] (15)

The hypothesis that no differences exist among the treatment groups was tested using an analysis of variance procedure on the ranked *T. vulpis* counts from worms recovered at necropsy. A significantly different and greater *T. vulpis* count was observed for the control group compared to the Drontal Plus Tablet group (P = .0010). No significant difference was detected between the control group and praziquantel + pyrantel tablet treatment group (P = 0.9288). A significantly different and greater *T. vulpis* count was detected for praziquantel + pyrantel treatment group as compared to the Drontal Plus Tablet treatment group (P = 0.0009).

Conclusion: Drontal Plus Tablets provided 94% removal of *T. vulpis* while praziquantel + pyrantel tablets were not efficacious against this parasite. This demonstrated that febantel is necessary in the combination for efficacy against *T. vulpis* (whipworms).

Table 6: Summary table of effectiveness (% efficacy) of all the anthelmintics used in the four laboratory investigations (see Agency Conclusions for a discussion of this table):

Drug	Study #	*A. caninum*	*U. stenoceph*	*T. canis*	*T. leonina*	*T. pisiformis*	*T. vulpis*
PP	1	99.48	-	95.4	-	-	0
PP	2	96	-	-	-	-	-
PP	3	-	85.3	-	95.74	-	-
F	4	84.5	-	15.07	-	97.66	42.3
P+PP	1	99.83	-	-	-	-	0
P+PP	2	80	74	95.97	-	-	-
P+PP	3	-	-	-	92.52	-	-
P+PP	4	100	-	100	-	100	0
P+PP+F	1	100	-	99.68	-	-	93.99
P+PP+F	2	99.6	99.8	-	-	-	-
P+PP+F	3	-	-	-	97.81	-	-
P+PP+F	4	98.41	-	92.99	-	100	91.31

F=febantel P=praziquantel PP=pyrantel pamoate

B. Pivotal Clinical Trials

1. Drontal Plus (praziquantel + pyrantel + febantel) Tablets Clinical Trial

A clinical trial was conducted with a common protocol by investigators at five geographic locations to provide additional information regarding Drontal Plus Tablets (the formulation to be marketed). The investigators are listed below:

Investigator	Location
Dr. R. Clark	Benton, Illinois
Drs. R. Hale and D. Wood	Little Rock, Arkansas
Dr. G. Hunt	Opelika, Alabama
Dr.T. Lamp	Bellville, Texas
Dr. R. Mauldin and C. Moe	Oklahoma City, Oklahoma

The purpose of this trial was to evaluate the efficacy and safety of Drontal Plus Tablets for treatment of dogs naturally infected with whipworms (Trichurisvulpis) plus other intestinal helminths under practical conditions in veterinary clinics. Pretreatment fecal samples from each dog were examined microscopically for diagnosis of parasite infections. Each animal served as its own control.

Two sizes of Drontal Plus tablets with the individual dosage tables recommended for the product to be marketed were utilized.

For small dogs (up to 25 lbs) - tablets containing 22.7 mg praziquantel, 22.7 mg pyantel base and 113.4 febantel/scored tablet.

Body Weight (Lb.)	Number of Tablets
2 - 7	1.0
8 - 12	1.5
13-19	2.0
19-25	2.5

For medium and large dogs (26 lbs. and over) - tablets containing 68.0 mg praziquantel, 68.0 mg pyrantel base and 340.2 mg febantel/scored tablet.

Body Weight (Lb.)	Number of Tablets
26-30	1.0
31-44	1.5
45-60	2.0
61-74	2.5
75-90	3.0
91-104	3.5
105-120	4.0

For dogs infected with tapeworms pretreatment, the feces of each dog was examined on Days 5, 6 and 7 after treatment to determine if the tapeworm infections were eliminated. Fecal samples were collected 7 - 10 days post-treatment to calculate the nematode egg count reduction.

The investigators treated a total of 103 purebred and mixed-breed dogs (48 males and 55 females) with Drontal Plus Tablets. No side effects following treatment (excellent rating) were reported for any of the 103 cases. The number of infections treated and the post-treatment results are given in Table 7.

Table 7 Drontal Plus Tablets Clinical Trial Efficacy Results

Parasite	No. of Infections Treated	Post-Treatment % Reduction of Mean Egg Counts	Post-Treatment % of Cases Cleared to Zero
Whipworms - *Trichuris vulpis*	98	94.5	89.8
Tapeworms - *Taenia pisiformis*	6	100	100
Tapeworms - *Dipylidium caninum*	28	100	100
Hookworms - *Ancylostoma caninum*	77	97.2	83.1
Hookworms - *Incinaria stenocephala*	1	100	100
Ascarids - *Toxocara canis*	6	89.5	83.3

Conclusion: Drontal Plus Tablets were efficacious for the removal of whipworm, tapeworm, hookworm and ascarid infections of dogs.

Summary of the Laboratory and Clinical Trial Results: The results of the pivotal clinical trial supported data collected during the four pivotal laboratory efficacy studies. Both praziquantel + pyrantel tablets and Drontal Plus (praziquantel + pyrantel + febantel) Tablets were efficacious against tapeworm infections. Neither pyrantel nor febantel interfered with the cestocidal activity of praziquantel against tapeworms. Praziquantel + pyrantel tablets and Drontal Plus Tablets were both efficacious against hookworms and ascarids. Praziquantel did not interfere with the nematocidal activity of pyrantel nor febantel. Praziquantel + pyrantel tablets were not efficacious for the removal of whipworms. The combined nematocidal activity of pyrantel and febantel, however, resulted in efficacious removal of whipworms. The recommended treatment of Drontal Plus Tablets was found to be safe and effective for the removal of the parasite species indicated on the label under conditions of practical use.

C. Corroborative Efficacy Studies

1. Drs. B. Bosch and J. Schroder, Kyalami, South Africa

Twenty dogs were experimentally infected with approximately 700 infective Ancylostoma caninum larvae. Seven days following the experimental infections 10 dogs were treated with praziquantel/pyrantel/febantel tablets to provide 5 mg/kg praziquantel + 5 mg/kg pyrantel base + 15 mg/kg febantel. Ten dogs were untreated controls. All of the dogs were euthanatized 21 days after treatment and examined for all remaining worms. The praziquantel/pyrantel/febantel treatment was 92.23% efficacious for removal of 7-day old A. caninum infections.

2. Praziquantel/Pyrantel Tablet Clinical Trial

A clinical trial was conducted with a common protocol by investigators at five geographic locations to provide additional information regarding performance of praziquantel + pyrantel tablets. The investigators are listed below:

Investigator	Location
Dr. D. Baker	Ft. Smith, Arkansas
Dr. C. Barnett	Stillwell, Kansas
Dr. T. Lamp	Bellville, Texas
Drs. R. Mauldin and C. Moe	Oklahoma City, Oklahoma
Drs. J. Wilson and R. Gill	Ripley, Tennessee

The purpose of this trial was to evaluate the efficacy and safety of praziquantel + pyrantel tablets for treatment of dogs naturally infected with tapeworms plus intestinal nematodes under practical conditions. Pretreatment fecal samples from each dog were examined microscopically for diagnosis of tapeworm and nematode infections. Each animalserved as its own control. Two sizes of praziquantel + pyrantel tablets with separate dosage schedules were provided to the investigators:

For small dogs (up to 25 lbs) - tablets containing 22.7 mg pyrantel base

Body Weight (Lb.)	Number of Tablets
2 - 7	1.0
8 - 12	1.5
13-18	2.0
19-25	2.5

For medium and large dogs (26 lbs. and over) - tablets containing 68.0 mg praziquantel and 68.0 mg pyrantel base.

Body Weight (Lb.)	Number of Tablets
26-30	1.0
31-44	1.5
45-60	2.0
61-74	2.5
75-90	3.0
91-104	3.5
105-120	4.0

The feces of each dog was examined on Days 5, 6 and 7 after treatment to determine if the tapeworm infections were eliminated. Fecal samples were collected 7 - 10 days post-treatment to calculate the nematode egg count reduction.

The investigators treated a total of 67 purebred and mixed-breed dogs (36 males and 31 females) with praziquantal + pyrantel tablets. Six dogs were not treated as specified in the protocol and data from those dogs were excluded for efficacy evaluation. One puppy weighing 1.2 lbs was given 1/2 of a 22.7 mg tablet (resulting in dosage levels of 21.0 mg/kg each of praziquantel and pyrantel) and died one day after treatment. The investigator concluded the death of this animal was a sequela to a severe parasite infection and was not caused by the experimental treatment.

Fifty-seven of the cases (93.4%) were rated excellent (no side effects observed) and 4 cases (6.6%) were rated good (single observance of a slight, self-limiting effect, i.e. vomition or loss of appetite). The number of parasite infections treated and the post-treatment results are given in Table 8.

Table 8. Praziquantel + Pyrantel Tablet Clinical Trial Efficacy Results

Parasite	No. of Infections Treated	Post-Treatment % Reduction of Mean Egg Counts	Post-Treatment of Cases Cleared to Zero
Tapeworms - *Taenia pisiformis*	10	100	100
Tapeworms - *Dipylidium caninum*	49	100	100
Hookworms - *Ancylostoma caninu*	50	98.8	90.0
Ascarids - *Toxocara canis*	19	84.4	73.7
Ascarids - *Toxascaris leonina*	4	85.7	50.0
Whipworms - *Trichuris vulpis*	8	13.9	25.0

Conclusion: Praziquantel + pyrantel tablets were efficacious for the removal of tapeworms, hookworms and ascarids of dogs. The tablets were not efficacious for removal of whipworms.

D. Overall Efficacy Summary

A total of 176 dogs and puppies with naturally acquired or experimental parasite infections were included in 4 well-controlled laboratory studies to establish the efficacy of Drontal™ Plus Tablets. In addition, 103 dogs and puppies were included in clinical field studies conducted in 9 veterinary clinics at different geographical locations throughout the United States to further evaluate safety and efficacy. These studies included dogs of various sizes, ages, and breeds. These studies demonstrated Drontal™ Plus Tablets are safe and efficacious for the removal of the parasite species indicated on the label when used as directed.

Results obtained in the laboratory and clinical studies indicate small numbers of hookworm and roundworm eggs may be passed in the feces for up to 7 days after treatment although the worms themselves were eliminated. A follow-up fecal examination should be conducted 2-4 weeks after treatment to determine the need for retreatment.

III. TARGET ANIMAL SAFETY

A. Pivotal Studies

Two preclinical safety studies were conducted in dogs by MILES Corporation, Animal Health Division with the praziquantel/pyrantel pamoate/febantel tablet formulation in accordance with Good Laboratory Practice Regulations.

1. Drug Tolerance Test (Drug Tolerance Test for the Use of Praziquantel/Pyrantel/Febantel Tablets in Dogs)

M. Kohlenberg of Shawnee Mission, Kansas, conducted a drug tolerance evaluation in 3 dogs using both the 22.7 mg praziquantel/22.7 mg pyrantel/113.4 mg febantel and the 68.0/68.0/340.2 mg tablets. This evaluation determined the effects of administering 10 times the anticipated label use rate of the tablet formulation in a single day. One female and one male dog received the treatment and the control received an equivalent number of placebo tablets. The study was blinded with the individual making clinical observations not being aware of the respective treatments. Furthermore, the laboratories conducting the clinical chemistry/hematology evaluations and histological readings were not informed of the treatments. Parameters of the study included clinical signs, body weights, clinical chemistries, hematology, gross pathology and histopathology. The study concluded 7 days post-treatment. Vomition was the only clinical sign observed. Slight weight gains were achieved during the study. No trends were seen in the post-treatment serum chemistry or hematology analyses with the exception of one dog with an elevated SGPT reading at 24 hours post-treatment, but this parameter had returned to normal at the 7 day sampling. The gross lesions (mesenteric lymph node redness and small intestinal mucosal redness in the two treated dogs) seen at necropsy could not be documented histopathologically and were not due to treatment with Drontal Plus. No microscopic changes were found in any of the tissues examined. It was concluded from this study that a single treatment of dogs with this praziquantel/pyrantel/febantel formulation at 10 times the label use rate can induce vomition without other adverse clinical effects. The results are summarized in Table 9.

Table 9. Drug Tolerance Test

Number of Animals	Treatment Rate	Clinical Observations
1	Control (Placebo Tablets)	Normal
1	52.8/52.8/263.7 mg/kg	Vomition at 3 and 24 hours
1	61.1/61.1/305.8 mg/kg	Vomition at 30 min. and 3 hours

2. General Safety Evaluation (General Safety Evaluation for the Use of Praziquantel/Pyrantel/Febantel Tablets in Dogs)

M. Kohlenberg also conducted a general safety study in 14 dogs using the 68.0/68.0/340.2 mg tablet. Two of the dogs, Group 1, were nontreated controls. Groups II, III and IV (4 animals/group) received 1, 3 and 5 times the recommend use rate, respectively, for 3 consecutive days (3 times the duration of treatment). Parameters evaluated were clinical signs, body weights, hematology, clinical chemistries, necropsy observations and histological readings. The study was completely blinded for the clinical sign observations, clinical laboratory procedures and histological readings. Body weights were stable during the study. Clinical signs were dose related and consisted of vomition and non-formed stools. No post-treatment trends were seen for the group mean values for the hematology and clinical chemistry parameters when compared to the pretreatment values or to those of nontreated controls with the exception of one dog in Group III which had elevated SGPT (549), SGOT (239), GGT (15) and CPK (285) readings at 6 days post-treatment. None of the findings at necropsy or upon histological examination were judged to be treatment related. It was concluded from this study that an adequate safety margin exists for the treatment of dogs with a combination

praziquantel/pyrantel/febantel tablet based upon these treatments of use rate, 3 times use rate and 5 times use rate for 3 times the labeled duration. The data are summarized in Table 10.

Table 10 General Safety Evaluation

Number of Animals	Treatment Rate	Clinical Observations
2	Control	Normal
4	Use Rate for 3 Days	Vomition in one
4	3 X Use Rate for 3 Days	Vomition in 2 and non-formed stool in 1
4	5 X Use Rate for 3 Days	Vomition in 3 and non-formed stool in 1

B. Corroborative Studies

Corroborative safety studies were conducted by Miles Inc, Agriculture Division, Animal Health Products in accordance with Good Laboratory Practice Regulations. Well controlled Corroborative Safety studies were also conducted by subsidiaries of Bayer AG, parent company of Miles Inc. Reference is also made to 3 NADA's containing one or more of the 3 components. Additionally, clinical field trial safety studies were conducted at veterinary clinics in various geographical areas of the United States.

1. Drug Tolerance Test (Drug Tolerance Test for the Use of Praziquantel/Pyrantel Tablets in Dogs)

M. Kohlenberg of Shawnee Mission, Kansas, conducted a drug tolerance evaluation in 3 dogs using a single massive overdose with this 68 mg/68 mg/praziquantel/pyrantel tablet formulation. A female and a male received a single treatment at 10 times the highest potential mg/kg treatment rate for the praziquantel/pyrantel tablets. The control animal received an equivalent number of placebo tablets. Parameters evaluated included clinical signs, body weights, clinical chemistries, hematology, gross pathology and histopathology. Post-treatment vomition was the only clinical sign observed for the treated dogs. Weights remained stable during the study. No post-treatment trends were observed for hematology and clinical chemistry parameters when compared to the pre-treatment values with the exception of one dog which had an elevated SGPT at 24 hours post-treatment. All tissues examined from all three dogs were within normal limits. It was concluded from this study that a single treatment of dogs with this praziquantel/pyrantel 68 mg/68 mg tablet at 10 times the highest possible mg/kg use rate induces vomition without other effects. The results are displayed in Table 11.

Table 11. Drug Tolerance Test

Number of Animals	Treatment Rate	Clinical Observations
1	Control (Placebo Tablets)	Normal
1	250/250 mg/kg	Vomition at 30 min. and 2 hours
1	250/250 mg/kg	Vomition at 30 min. and 2 hours

2. General Safety Evaluation (General Safety Evaluation for the Use of Praziquantel/Pyrantel Tablets in Dogs)

M. Kohlenberg also evaluated the general safety of the 68 mg pyrantel/68 mg praziquantel tablets in 16 dogs. Parameters evaluated included clinical signs, body weights, clinical chemistries, hematology, gross pathology and histopathology. Four of the dogs, Group 1, were nontreated controls. Groups II, III and IV (4 animals/group) received, 1, 3 and 5 times the recommended dosage rate, respectively, for 3 consecutive days (3 X duration of treatment). No clinically significant signs were observed. Body weights were stable during the study. No trends were seen in the serum chemistry or hematology values at post-treatment intervals. The gross lesions (redness of the lung) seen at necropsy were not due to treatment with pyrantel/praziquantel. The histopathological lesions (interstitial pneumonia, vascular congestion) were not due to treatment with praziquantel/pyrantel. It was concluded from this study that treatment of dogs with this praziquantel/pyrantel formulation at 5 times the label use rate for 3 times the recommended duration of treatments without adverse effects. The results are displayed in Table 12.

Table 12. General Safety Evaluation

Number of Animals	Treatment Rate	Clinical Observations
4	Control	-
4	Use Rate for 3 Days	-
4	3 X Use Rate for 3 Days	-
4	5 X Use Rate for 3 Days	One dog in the 5X group vomited 3 daysafter the third dose

3. Dosage Tolerance Study, Drs. B. Bosch and J. Schroder, Kyualami, South Africa

Twenty-seven puppies between 9 and 13 weeks of age were divided into 3 groups. Ten puppies were treated orally with praziquantel/pyrantel tablets to provide 15 mg/kg praziquantel + 15 mg/kg pyrantel base, 10 puppies received praziquantel/pyrantel/febantel tablets to provide 15 mg/kg praziquantel/43.2 mg/kg pyrantel base + 45 mg/kg febantel. Seven puppies remained as untreated controls. All puppies were observed daily for 7 days after treatment.

One puppy treated with praziquantel/pyrantel tablets had loose feces for 48 hours after treatment. One puppy treated with praziquantel/pyrantel/febantel tablets had loose feces on the day of treatment and for 48 hours after treatment.

The praziquantel/pyrantel and praziquantel/pyrantel febantel tablets were concluded to be safe for puppies at approximately 3 times the recommended dosage rate.

4. Dosage Tolerance Study, Drs. T. Hopkins and P. Gyre, Bahrs Hill, Australia

Two puppies 17 days old were treated with praziquantel/pyrantel/febantel tablets to provide approximately 17 mg/kg praziquantel + 48 mg/kg pyrantel base + 83.3 mg/kg febantel. Two additional puppies served as untreated controls. The puppies were observed for 4 hours after treatment. No adverse reactions were observed and the treatments were concluded to be safe at 3-5X the recommended dosages.

5. Dosage Tolerance Study, Drs. T. Hopkins, L. Griffin, P. Gyre and P. Hedemann, Bahrs Hill, Australia

Two litters of puppies with 6 males in each were randomly allocated to 2 groups of 3 within each litter. One group (6 puppies) received praziquantel/pyrantel/febantel oral dosage rates of approximately 20 mg/kg praziquantel + 20 mg/kg pyrantel base + 60 mg/kg febantel at 2, 4, 6, 8, 10, 12, 25 or 26 and 40 or 41 weeks of age (a total of 8 treatments). The other group of 6 puppies served as untreated controls. The puppies were observed for any clinical abnormalities from 2 to 49 weeks of age. Semen collections were made when the dogs were 294-334 days old. At 49-50 weeks of age the dogs were euthanatized and necropsied.

Clinical abnormalities (alkaline phosphatase level higher in the treated group compared to the control group, lactic dehydrogenase levels also higher in the treated group at one test interval) were not related to treatment with the test article and it was concluded that the multiple dosages of approximately 2-4X the recommended dosages of praziquantel/pyrantel/febantel tablets had no significant effect on the health or semen production of the animals.

6. Oral Tolerance and Safety Study, Drs. T. Hopkins and P. Gyre, Bahrs Hill, Australia.

Six 2 week old puppies were treated orally with praziquantel/pyrantel/febantel tablets to provide dosage ranges of 20-40 mg/kg praziquantel (4X), 57-115 mg/kg pyrantel base (6-12X) and 208.3- 337.8 mg/kg febantel (8-13X). One week later 4 of the puppies were treated with dosage ranges of 20.8-33.8 mg/kg praziquantel (5-7X) + 20.8-33.8 mg/kg pyrantel base (4-7X) + 104.1-168.9 mg/kg febantel (3-5X) and 2 of the puppies were treated with placebo tablets. The puppies were observed for 4 hours after each treatment and the animals were necropsied 24 hours after the second treatment. Multiple vomiting was observed in all puppies treated with praziquantel/pyrantel/febantel tablets from 30 minutes to 4 hours after treatment. No abnormalities were observed in puppies treated with placebo tablets. No microscopic lesions were noted at necropsy.

7. Confirmation of Safety in Clinical Field Trials (Praziquantel/Pyrantel Pamoate)

Confirmation of safety for the use of praziquantel/pyrantel pamoate tablets in dogs was achieved in clinical field trials. Five veterinary clinics in various geographical locations treated a total of 61 dogs as per the label dosage schedule. The 61 dogs treated were in an age range of 2 months to 14 years with a weight range of 1.2 to 110 pounds. Both males and females were included and breeds were representative. The clinical veterinarians rated overall safety as excellent for 57 (93.4%) and good for 4 (6.6%) of the dogs treated. One of the 4 dogs had diarrhea once the day following treatment, another had a loose stool with tapeworm segments for 2 days after treatment and a third vomited once 2 days after treatment. The fourth dog vomited 6 days after treatment, but the investigator noted the dog had consumed a foreign material before this occurred.

Numerous types of other animal health products were administered to 19 of the dogs concurrently or within 48 hours of the praziquantel/pyrantel pamoate treatments. These products include sedatives, anesthetics, antibiotics, corticosteroids and vaccinations with no incompatibility observed. in conclusion, the clinical field trial

safety evaluations substantiated an adequate safety margin and confirmed findings of the preclinical target animal safety studies.

8. Confirmation of Safety in Clinical Field Trials (Praziquantel/Pyrantel Pamoate/Febantel)

Confirmation of safety for the use of Drontal Plus Anthelmintic Tablets (praziquantel/pyrantel pamoate/febantel) in dogs was achieved in clinical field trials. Five veterinary clinics in various geographical locations treated a total of 103 dogs as per the label dosage schedule. The dogs were in an age range of 2 months to 16 years with a weight range of 5 to 110 pounds. Both males and females were included and breeds were representative. The clinical veterinarians rated overall safety as excellent (no side effects observed) for all of the treatments (100%). Other animal health products were administered concurrently within 48 hours to 16 of the dogs with no incompatibility. These products were primarily antibiotics and vaccinations. In conclusion, the clinical field trial safety evaluations substantiated an adequate safety margin for the treatment of dogs with Drontal Plus.

9. Reference to NADA 111-798

Safety for the treatment of dogs with a tablet formulation of praziquantel was evaluated and presented in NADA 111-798. This NADA concerned Droncit Canine Cestocide Tablets and contained 9 preclinical safety studies conducted under GLP regulations. These studies demonstrated the safety of Droncit Cestocide Tablets in the treatment of tapeworms in dogs.

10. Reference to NADA 133-953

Safety for the treatment of dogs with febantel alone or febantel combined with praziquantel was evaluated in well controlled preclinical studies and clinical field trials as previously presented in NADA 133-953. This NADA concerned Vercom Broad Spectrum Anthelmintic Paste containing 3.4% febantel and 0.34% praziquantel. NADA 133-953 contained 7 preclinical safety studies conducted in dogs with febantel as a single component and 7 evaluations with febantel in combination with praziquantel. All studies were conducted under GLP regulations. These studies demonstrate the safety of Vercom Paste® when used to remove nematode and cestode parasites from dogs and puppies.

11. Reference to NADA 140-912

Safety for the treatment of dogs and puppies with febantel was further evaluated in well controlled preclinical studies and clinical field trials as earlier presented in NADA 140-912. This NADA concerned Rintal Tabs containing either 27.2 or 163.3 mg febantel. NADA 140-912 contained 2 preclinical safety studies conducted in dogs with febantel as per GLP regulations. These studies demonstrated the safety of Rintal Tabs in the treatment of nematode in dogs.

IV. HUMAN FOOD SAFETY

A. Human Food Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The formulation is labeled for use in dogs only.

B. Safety Relative to Possession, Handling and Administration

The label contains an adequate warning statement: "Warning: Keep Out of Reach of Children"

V. AGENCY CONCLUSIONS

The data in support of this original NADA complies with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Drontal Plus® (praziquantel + febantel + pyrantel pamoate) tablets when used under the labeled conditions of use are safe and effective.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval for non- food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of whipworm and hookworm infections and to differentiate the type of tapeworm infection. The differentiation of the type of tapeworm infection is necessary for proper preventative control procedures to be initiated or reinforced.

All three of the drug components in this combination are approved individually. Pyrantel pamoate is approved for *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, and *Ancylostoma caninum*. Praziquantel is approved for *Taenia pisiformis*, *Echinococcus. granulosus*, and *Dipylidium caninum*. Febantel is approved for *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, *Ancylostoma caninum*, and *Trichuris vulpis*. A two-way combination consists of praziquantel + febantel (Vercom ® paste) and is approved for *Taenia pisiformis*, *Dipylidium caninum*, *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, *Ancylostoma caninum*, and *Trichuris vulpis*. Safety and efficacy information is available on all three components of this combination.

The Guideline for Drug Combinations is generally applied to new drug formulations. The Guideline states that a 3-way combination must be better than all possible 2-way combinations of the same three drugs. All possible two-way combinations were not studied, but it was established that the three-way combination is superior to the two-way combination (praziquantel + febantel) and to pyrantel alone. It was also demonstrated that each of the components did not interfere with the effectiveness of the others. Hence, although the Guideline was not strictly met, the combination of praziquantel + pyrantel pamoate + febantel is approvable based on the following justification:

1) Evidence was provided to show that each ingredient designated as active in the combination made a contribution to the effect in the manner claimed or suggested in the labeling. Each component drug contributes to the efficacy of the product which cannot be achieved with any two-way combination which was studied.

2) Pyrantel pamoate and febantel provide synergistic nematocidal activity. Febantel is the only drug in the combination effective against whipworms (*T. vulpis*). The combination of pyrantel pamoate and febantel in the 3-way combination provides enhanced efficacy against whipworms (94% and 91.31%), whereas febantel alone only provided 42.30% efficacy. The pyrantel pamoate component alone provides

higher efficacy against the nematodes than febantel, except for whipworms, demonstrating the need for pyrantel pamoate in the combination.

3) Although febantel demonstrated some efficacy against the tapeworm *Taenia pisiformis*, praziquantel is necessary in the combination for 100% efficacy against *E. granulosus* (febantel has no efficacy against this parasite) and for 100% removal of *T. pisiformis* and *D. caninum* (refer to NADA 133-953, Vercom® paste and NADA 111-798, Droncit®). The sponsor provided documentation that febantel demonstrates weak and erratic efficacy against *D. caninum* and *T. pisiformis*.

4) Each drug in the combination provides a different mechanism of parasiticidal action, as described in the labeling. This is important as parasites may develop resistance to some anthelmintics over time.

5) The convenience of a single tablet formulation (as opposed to a paste or liquid formulation) which is effective against a broad range of parasites is important to veterinary clients, for ease and compliance with administration of the correct dosage.

There are no known safety or efficacy issues pending with regard to either pyrantel pamoate, praziquantel, or febantel.

It was not necessary to titrate a dose for pyrantel for this NADA package, since the sponsor demonstrated efficacy against all four species of parasites (*Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, and *Ancylostoma caninum*), claimed on the label. Efficacy of greater than 90% was achieved in the laboratory dose confirmation/efficacy studies, except for Uncinaria stenocephala (85.3% efficacy). However, the literature documents inconsistent efficacy with pyrantel pamoate and the 3-way combination achieved 99.8% efficacy against this parasite.

In conclusion, the 3-way combination of praziquantel, pyrantel pamoate, and febantel provides an effective, convenient tablet for use against a broad range of parasites. Each component of the combination is justified.

VI. Labeling

1) Base label, small dogs, printed 150%, 50 tablet count

2) Fix-a-form insert, first section, 50 tablet bottle, small dogs

3) Fix-a-form insert, second section, 50 tablet bottle, small dogs

4) Inner shipper, 50 ct. bottle, small dogs

5) Outer shipper, 50 ct. bottle , small dogs

6) Base label, printed 150%, small dogs, 150 tablet counts

7) Fix-a-form insert,150 tablet bottle, small dogs

8) Inner shipper, 150 ct. bottle

9) Outer shipper, 150 ct. bottle

10) Foil strip front, small dogs, printed 100%

11) Foil strip back, small dogs, printed 100%

12) Dispensing carton, small dogs, reduced 35%

13) Foil tablet dispensing carton, small dogs, reduced 35%

14) Shipper, 2 X 5 foil strips, small dogs

15) Base label, medium and large dogs, 50 tablets, printed 150%

16) Fix-a-form insert, 50 tablet bottle, large dog tablets

17) Inner shipper, 50 ct. bottle, medium and large dogs

18) Outer shipper, 50 ct. bottle, medium and large dogs

19) Base label, medium and large dogs, 150 tablets, printed 125%

20) Fix-a-form insert, medium and large dogs, 150 tablets, 80%

21) Outer shipper, 150 ct. bottles, medium and large dogs

22) Foil tablet dispensing carton, large dogs, page 1

23) Foil tablet dispensing carton, large dogs, page 2

24) Dispensing envelope, printed 100%

25) Multi-leaflet, printed 100%

26) Shipper, 2 X 5 foil strips, large dogs

27) Foil strip front, medium and large dogs, printed 100%

28) Foil strip back, medium and large dogs, printed 100%

Copies of these labels may be obtained by writing to the:
Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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