Date of Approval: January 12, 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-007

DRONTAL Plus TASTE TABS

(praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic Tablets for Dogs

1) For the removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*).

2) For the removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs.

Sponsored by:
Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66202

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number: NADA 141-007

b. Sponsor: Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

Drug Labeler Code: 000859

c. Established Name: praziquantel/pyrantel pamoate/febantel

d. Proprietary Name: DRONTAL Plus TASTE TABS

e. Dosage Form: Chewable Tablet

f. How Supplied: DRONTAL Plus TASTE TABS are supplied in blister packs by the carton as follows:
Puppies and Small Dogs: 4 strips of 10 tablets (40 tabs/carton)
Medium Sized Dogs: 4 strips of 10 tablets (40 tabs/ carton)
Large Dogs: 3 strips of 10 tablets (30 tabs/carton)

g. How Dispensed: Rx

h. Amount of Active Ingredients: Each tablet for Puppies and Small Dogs contains: 22.7 mg praziquantel, 22.7 mg pyrantel base as pyrantel pamoate, and 113.4 mg febantel.

Each tablet for Medium Dogs contains: 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate, and 340.2 mg febantel.

Each tablet for Large Dogs contains: 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate, and 680.4 mg febantel.

i. Route of Administration: Oral

j. Species/Class: Canine

k. Recommended Dosage: The presence of parasites should be confirmed by laboratory fecal examination. Weigh the animal before treatment. Administer the proper dosage as specified in the following table as a single treatment.

DRONTAL Plus TASTE TABS Dosage Chart

Puppies/Small Dogs* (2 – 25 lbs)		Medium Sized Dogs (26 – 60 lbs)		Large Dogs (45 lbs and greater)	
Body Wt. (lbs)	Taste Tabs	Body Wt. (lbs)	Taste Tabs	Body Wt (lbs)	Taste Tabs
2 - 4	0.5	26 – 30	1.0	45 – 60	1.0
5 – 7	1.0	31 – 44	1.5	61 – 90	1.5
8 – 12	1.5	45 – 60	2.0	91 – 120	2.0
13 – 18	2.0				
19 – 25	2.5				

*Not for Use in Puppies Less Than 3 Weeks of Age or Dogs Weighing Less Than 2 lbs.

The tablet sizes and dosage table are designed to provide a minimum of 5.0 mg/kg (2.27 mg/lb) each of praziquantel and pyrantel base, and at least 25 mg/kg (11.35 mg/lb) febantel.

The tablets may be offered to the dog by hand. Alternatively, tablets may be given directly by mouth or offered in a small amount of food. Fasting is neither necessary nor recommended prior to or after treatment.

l. Pharmaceutical Category: Anthelmintic

m. Indications: DRONTAL Plus (praziquantel/pyrantel pamoate/febantel) TASTE TABS Broad Spectrum Chewable Anthelmintic Tablets are indicated for the removal of Tapeworms (*Dipylidium caninum, Taenia pisiformis, Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*) and for removal of Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), Ascarids (*Toxocara canis, Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs.

n. Effect of Supplement: This supplement amends the approved NADA by adding a flavored tablet formulation with the same indications.

2. EFFECTIVENESS:

The effectiveness of DRONTAL Plus TASTE TABS is based upon the existing approvals for DRONTAL Plus tablets (NADA 141-007). In addition, four well-controlled laboratory studies were conducted to confirm that the anthelmintic effectiveness of flavored DRONTAL Plus TASTE TABS is equivalent to the original unflavored formulation. One study was designed to evaluate effectiveness of the DRONTAL Plus TASTE TABS against helminths occupying the upper intestinal tract (hookworms). Three studies were conducted according to a common protocol to evaluate the effectiveness of the DRONTAL Plus TASTE TABS against helminths occupying the lower intestinal tract (whipworms). A field study was conducted to confirm palatability.

A. Evaluation of DRONTAL Plus TASTE TABS Against Hookworm Infection of Dogs, Study No. 151.657.

The purpose of this well-controlled anthelmintic study was to confirm the effectiveness of DRONTAL Plus TASTE TABS against experimental hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections of dogs.

Investigator: Robyn Slone, B.S.
Professional Laboratory and Research Service
Corapeake, NC

Animals: Twenty purpose bred beagles (10 male, 10 female), 2 – 2½ months of age.

Dosage Groups:

Group 1: DRONTAL Plus TASTE TABS treated according to the labeled dosage to provide at least 5 mg/kg each of praziquantel and pyrantel base plus at least 25 mg/kg febantel (10 dogs).

Group 2: Untreated (10 dogs)

Route of Administration: Oral

Frequency of Treatment: Once

Duration of Study: 35 days

Study Design: Each dog was experimentally infected with a combination of *A. caninum* and *U. stenocephala* third stage larvae on test day –28. On test day –1 the twenty dogs were randomized into two groups by sex and body weight. On test day 0 group 1 dogs were treated with DRONTAL Plus TASTE TABS according to the label dosage. Group 2 dogs were untreated. On test day 7 the animals were euthanized for recovery of all remaining hookworms.

Parameters Measured: The geometric mean number of each hookworm species/dog recovered at necropsy from both study groups was determined. Percent effectiveness was calculated by comparing the geometric mean number of worms remaining in the DRONTAL Plus TASTE TABS treated group with the geometric mean number of worms retained in the control group.

Results: Adequacy of parasite infections was confirmed in the untreated control dogs. At necropsy adult *A. caninum* and *U. stenocephala* were recovered from all 10 control dogs. (*A. caninum* = 8 - 24 worms/dog, geometric mean = 16.60 worms/dog; *U. stenocephala* = 8 -16 worms/dog, geometric mean = 13.02 worms/dog). By contrast no *A. caninum* and only one *U. stenocephala* were recovered at necropsy from the 10 dogs treated with DRONTAL Plus TASTE TABS (geometric mean *A. caninum* and *U. stenocephala* counts of 0.0 and 0.07 worms/dog, respectively). Anthelmintic effectiveness of DRONTAL Plus TASTE TABS against *A. caninum* and *U. stenocephala* was 100 and 99.4%, respectively.

Adverse Reactions: One episode of bloody/mucoid stool occurred in a treated puppy on day 1. One episode of watery/profuse stool occurred in a treated puppy on day 3.

Conclusions: A single dose of DRONTAL Plus TASTE TABS administered orally according to the recommended dosage schedule was efficacious against helminths (*i.e.*, *A. caninum* and *U. stenocephala*) residing in the upper intestinal tract of dogs.

B. Evaluation of DRONTAL Plus TASTE TABS Against Natural *Trichuris vulpis* Infections of Dogs, Study Nos. 151.656, 151.682, 151.696.

The effectiveness of DRONTAL Plus TASTE TABS against dogs naturally infected with *Trichuris vulpis* (whipworms) was confirmed with three studies conducted according to a common protocol by two investigators at two study locations. Data from these studies were pooled for final effectiveness confirmation.

Investigators: Dawie Kok, D.Sc (Study 151.656)
Clinvet International (Pty)
Bloemfontein, South Africa

Dwight Bowman, Ph.D. (Studies 151.682, 151.696)
Cheri Hill R&D
Stanwood, MI

Animals: 60 dogs with natural *T. vulpis* infections.

Dosage Groups:

Group 1: DRONTAL Plus TASTE TABS treated according to the labeled dosage to provide at least 5 mg/kg each of praziquantel and pyrantel base plus at least 25 mg/kg febantel (30 dogs).

Group 2: Untreated (30 dogs)

Route of Administration: Oral

Duration of Study: 35 days

Study Design: Each dog was naturally infected with *T. vulpis* as confirmed by pretreatment fecal examination. On test day –1 the dogs were randomized into two treatment groups by sex and body weight. On test day 0, group 1 dogs were treated with DRONTAL Plus TASTE TABS according to the labeled dosage. Group 2 dogs were untreated. On test day 7 the animals were euthanized for recovery of all remaining *T. vulpis*.

Parameters Measured: The geometric mean number of *T. vulpis*/dog recovered at necropsy from both study groups was determined. Percent effectiveness was calculated by comparing the geometric mean number of worms remaining in the DRONTAL Plus TASTE TABS treated group with the geometric mean number of worms remaining in the in the control group.

Results: Adequacy of parasite infections was confirmed in the untreated control dogs. At necropsy, adult *T. vulpis* were recovered from all 30 control dogs (5-560 *T. vulpis* /dog). Table 1 below lists the geometric means for the treated and control groups in each of the three studies. Data from these studies were pooled for final effectiveness confirmation. Anthelmintic effectiveness of DRONTAL Plus TASTE TABS for removal of *T. vulpis*, as calculated with compiled data from the three studies, was 90%.

Table 1: Geometric Means and Effectiveness Percentages from Three Whipworm Effectiveness Studies

Study Number	Geometric Mean of Treated Group	Geometric Mean of Untreated Control Group	% Effectiveness
151.656	8.65	60.64	85.74
151.682	3.95	46.87	91.57
151.696	3.93	46.25	91.50

Adverse Reactions: One dog treated with DRONTAL Plus TASTE TABS vomited its tablet dosage within minutes of treatment and was redosed. One dog treated with DRONTAL Plus TASTE TABS vomited within 18 hours of treatment. No other unusual observations or adverse events were observed in any of the dogs during the study.

Conclusions: A single dose of DRONTAL Plus TASTE TABS administered orally according to the recommended dosage schedule, was efficacious against intestinal helminths (i.e. *T. vulpis*) residing in the lower intestinal tract of dogs.

C. Clinical Evaluation of the Palatability of DRONTAL Plus TASTE TABS for Dogs, Study No. 151.551.

The purpose of this field study was to confirm that palatability of DRONTAL Plus TASTE TABS in privately owned dogs.

Investigators:

Laird Laurence, D.V.M.
Fredericksburg, TX

Richard Mauldin, D.V.M.
Oklahoma City, OK

Roger Sifferman, D.V.M.
Springfield, MO

Animals: One hundred and fifty-one (151) client owned dogs between 6 months and 14 years of age, weighing between 3.8 pounds and 190 pounds. There were 86 females (61 spayed) and 65 males (42 neutered) representing 34 different breeds. Endoparasite infection was not required for enrollment.

Dosage Group: DRONTAL Plus TASTE TABS were offered to all of dogs according to the labeled dosage, which provides at least 5 mg/kg each of praziquantel and pyrantel base, plus at least 25 mg/kg febantel.

Route of Administration: Oral

Frequency of Treatment: Once

Duration of Study: One day for each dog

Study Design: DRONTAL Plus TASTE TABS were dispensed to owners based on the body weight of their dog(s). Approximately half of the dogs were dispensed whole tablets, and half were dispensed either partial tablets or a combination of whole and partial tablets for testing purposes. DRONTAL Plus TASTE TABS were offered to the pet by the owner at home. Tablets were offered by hand for up to two minutes, and if not consumed in this manner were then placed in a food bowl for an additional two minutes.

Parameters Measured: The dog owner scored the acceptance of the DRONTAL Plus TASTE TABS as follows:
1) All Tablets Consumed
2) No Tablets Consumed
3) Part of Tablets Consumed

Results: Acceptance of DRONTAL Plus TASTE TABS was scored as a success if the dog voluntarily ingested and consumed all of the DRONTAL Plus TASTE TABS within the four minutes the tablets were offered (an owner score of 1). Acceptance was scored as a failure if the tablet(s) were only partially consumed, or if no tablets were consumed within four minutes (an owner score of 2 or 3). Owners reported acceptance scores for 149 of the 151 dogs enrolled. Of these 149 dogs, a total of 133 dogs accepted DRONTAL Plus TASTE TABS (an owner score of 1), for a palatability success rate of 89.3%.

Adverse Reactions: One dog vomited 30 minutes after treatment, and another dog vomited 3 hours following treatment.

Conclusion: DRONTAL Plus TASTE TABS are palatable to dogs of various breeds, weights, and age.

3. TARGET ANIMAL SAFETY:

The approval of DRONTAL Plus TASTE TABS required no new target animal safety data as the formulation contains the same amount of active ingredients as the currently approved unflavored DRONTAL Plus Tablets. The approval of the TASTE TABS formulation is based on the effectiveness studies, chemistry, manufacturing and control information, and stability data.

4. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA supplement. Human warnings are provided on the product label as follows: "Keep out of reach of children."

5. 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 of the implementing regulations. The data demonstrate that DRONTAL Plus TASTE TABS when used under the labeled conditions of use are safe and effective for the removal of tapeworms (*Dipylidium caninum, Taenia pisiformis, Echinococcus granulosus,* and removal and control of *Echinococcus multilocularis*), and for removal of Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), Ascarids (*Toxocara canis, Toxascaris leonina*), and Whipworms (*Trichuris vulpis*) in dogs.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to manage the serious public health concerns associated with the diagnosis and treatment of *Echinococcus granulosus and multilocularis*.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new palatable formulation for which this supplement is approved. The four laboratory studies conducted by the sponsor to demonstrate substantial evidence of effectiveness for the new palatable formulation provided the basis for exclusivity.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

A U.S. patent for DRONTAL Plus TASTE TABS has been applied for. The application is pending.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

a) Package insert

b) Blister labeling
   1. Small
   2. Medium
   3. Large

c) Dispensing carton
   1. Small
   2. Medium
   3. Large