

Approval Date: FEB 10 2003

FREEDOM OF INFORMATION SUMMARY

NADA 141-007

Drontal® Plus Tablets
(Praziquantel/pyrantel pamoate/febantel)

- 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 Corporation Agricultural Division
Animal Health
P.O. Box 390
Shawnee Mission Kansas 66202

FREEDOM OF INFORMATION SUMMARY**1. GENERAL INFORMATION:**

- a. File Number: NADA 141-007
- b. Sponsor: Bayer Corporation
Agricultural Division
Animal Health
P.O. Box 390
Shawnee Mission Kansas 66202
Drug Labeler Code: 000859
- c. Established Name: Praziquantel, pyrantel pamoate, febantel
- d. Proprietary Name: Drontal® Plus Tablets
- e. Dosage Form: Tablet
- f. How Supplied: Each tablet size is available in bottles of 50 tablets (puppies and small dogs, medium sized dogs) or 30 tablets (large dogs).
Code 08713130-176099 50 tablets/bottle (Puppies and Small Dogs)
Code 08713149-177099 50 tablets/bottle (Medium Sized Dogs)
Code 08724639 30 tablets/bottle (Large Dogs)
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: The currently approved tablet sizes contain 22.7 mg, 22.7 mg and 113.4 mg (Puppies and Small Dogs) and 68.0 mg, 68.0 mg, 340.2 mg (Medium Sized Dogs) each of praziquantel, pyrantel base as pyrantel pamoate, and febantel respectively. The proposed new tablet (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 large size tablet size is administered as specified in the following table as a single oral treatment.

<u>Body Weight (lbs.)</u>	<u>Number of Tablets</u>
45-60	1.0
61-90	1.5
91-120	2.0

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. Pharmacological Category: Anthelmintic
- m. Indications: Drontal® Plus Tablets are indicated for the removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*). Drontal® Plus Tablets are also indicated for the 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 NADA to provide for a larger tablet containing 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate and 680.4 mg febantel and the associated label changes.

2. **EFFECTIVENESS:**

The approval of the larger size tablet containing praziquantel (136.0 mg), pyrantel base (136.0 mg) as pyrantel pamoate, and febantel (680.4 mg) tablet does not require new effectiveness data as the minimum dose remains the same as currently approved. The approval is based on the manufacturing information on containers/closures, labeling, dissolution and stability of the new larger size tablets.

3. **TARGET ANIMAL SAFETY:**

The approval of the larger size tablet containing praziquantel (136.0 mg), pyrantel base (136.0 mg) as pyrantel pamoate, and febantel (680.4 mg) tablet does not require new target animal safety data as the maximum dose remains the same as currently approved. The approval is based on the manufacturing information on containers/closures, labeling, dissolution and stability of the new larger size tablets.

4. **HUMAN 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, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

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 demonstrates that Drontal® Plus tablets, when administered orally, are safe and effective for the removal of tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*), the removal of hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), ascarids (*Toxocara canis*, *Toxascaris leonina*) and whipworms (*Trichuris vulpis*) in dogs.

This supplement is a Category II change under the Center's supplemental approval policy, 21 CFR 514.106(b)(2). 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.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

Drontal® Plus Tablets are under the following U. S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
5,036,069	July 30, 2008

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

- a. Bottle label for large, medium and small dog sizes.
- b. Case label for large, medium and small dog sizes.
- c. Package insert for large, medium and small dog sizes.

Lot No.:
Exp. Date:
08724638

For removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, *Echinococcus multilocularis*) and control of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*) and Whipworms (*Trichuris vulpis*) in dogs. **DOSAGE AND ADMINISTRATION:** Administer the proper dose as specified in the following table as a single oral treatment.

Body Weight (lbs.)	Number of Tablets
45 - 60	1.0
61 - 90	1.5
91 - 120	2.0

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.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Consult package insert for further details.

08724638
NADA 141-007, Approved by FDA

1-800-333-3333

Drontal® Plus
(praziquantel/pyrantel pamoate/febantel)
Tablets

30 Tablets

Bayer

Bayer Corporation, Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-007, Approved by FDA

Broad Spectrum Anthelmintic
For Large Dogs (45 lbs and greater)

Lot No.:
Exp. Date:
08713130-177069

For removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*). For removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs. **DOSAGE AND ADMINISTRATION:** Administer the proper dose as specified in the following table as a single oral treatment.

Body Weight (lbs.)	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 PUPPIES LESS THAN 2 WEEKS OF AGE OR DOGS WEIGHING LESS THAN 2 LBS.** 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. **CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS.** Consult package insert for further details.

08713130-177069 08714927-71017800, R.6

LEAFLET PLACEMENT

Lot No.:
Exp. Date:
08713149-177069

For removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*). For removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs.

DOSAGE AND ADMINISTRATION: Administer the proper dose as specified in the following table as a single oral treatment.

Body Weight (lbs.)	Number of Tablets
26 - 30	1.0
31 - 44	1.5
45 - 60	2.0

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.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Consult package insert for further details.

08713149-177069 08714935-71017700, R.6

Drontal® Plus
(praziquantel/pyrantel pamoate/febantel)
Tablets

Broad Spectrum Anthelmintic
For Medium Sized Dogs (26-60 lbs.)

CAUTION: Do not use in puppies with less than 2 weeks of age, the order of a Scaevola or thyme, or in animals less than 2 weeks of age.

50 Tablets
Bayer

Bayer Corporation, Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-007, Approved by FDA

Drontal[®] Plus

Code 08713130-176099

(Praziquantel/Pyrantel Pamoate/Febantel)

Anthelmintic Tablets for Puppies and Small Dogs

Store at controlled room temperature between 59-86° F (15-30° C)

72 X 50 Tablets

Bayer 

Lot: 000000A

Exp: OCT 02

**Bayer Corporation,
Agriculture Division, Animal Health,
Shawnee Mission, Kansas 66201**

Made In USA R.2

Drontal[®] Plus Code 08713149-177099

(Praziquantel/Pyrantel Pamoate/Febantel)

Anthelmintic Tablets for Medium Sized Dogs

Store at controlled room temperature between 59-86° F (15-30° C)

72 X 50 Tablets

Bayer 

Lot: 000000A

Exp: OCT 02

**Bayer Corporation,
Agriculture Division, Animal Health,
Shawnee Mission, Kansas 66201**

Made In USA R.2

Drontal[®] Plus

Code 08724639

(Praziquantel/Pyrantel Pamoate/Febantel)

Anthelmintic Tablets for Large Dogs

Store at controlled room temperature between 59–86° F (15–30° C)

12 X 30 Tablets

Bayer 

Lot: 000000A

Exp: OCT 02

**Bayer Corporation,
Agriculture Division, Animal Health,
Shawnee Mission, Kansas 66201**

Made In USA R.O

Large dog insert

Drontal® Plus
(praziquantel/pyrantel pamoate/febantel)
Tablets
Broad Spectrum Anthelmintic for Dogs

DESCRIPTION: Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Anthelmintic Tablets are available in three sizes. Each size is scored for convenient oral administration. Each Drontal® Plus Tablet for Puppies and Small Dogs contains 22.7 mg praziquantel, 22.7 mg pyrantel base as pyrantel pamoate and 172.4 mg febantel.

Each Drontal® Plus Tablet for Medium Sized Dogs contains 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate and 516.2 mg febantel.

Each Drontal® Plus Tablet for Large Dogs contains 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate, and 1032.4 mg febantel.

ACTION: Drontal® Plus Tablets contain three active ingredients having different modes of action and spectra of activity. Praziquantel is active against cestodes (tapeworms). Praziquantel is absorbed, metabolized in the liver and excreted in the bile. Upon entering the digestive tract from the bile, cestodal activity is exhibited. Following exposure to praziquantel, the tapeworm loses its ability to resist digestion by the mammalian host. Because of this, whole tapeworms, including the scoleces, are very rarely passed after administration of praziquantel. In many instances, only scoleces and partially digested pieces of tapeworms will be seen in the stool. The majority of tapeworms are digested and are not found in the feces.

Pyrantel pamoate is active against hookworms and ascarids. Pyrantel pamoate acts on the cholinergic receptors of the neuromuscular resulting in spastic paralysis. Paralytic action of the intestinal tract then eliminates the parasite.

Febantel is active against nematode parasites including whipworms. Febantel is rapidly absorbed and metabolized in the animal. Available information suggests that the parasite's energy metabolism is blocked, leading to energy exchange breakdown and inhibited glucose uptake.

Laboratory efficacy and clinical studies conducted with Drontal® Plus Tablets demonstrate that each of the three active ingredients act independently without interference. The combined tablet formulation provides a wide spectrum of activity against the indicated species of intestinal helminths.

INDICATIONS: Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Anthelmintic Tablets are indicated for removal of tapeworms (*Dipylidium caninum*, *Taenia polydesma*, *Echinococcus granulosus*, and mixed and exotic *Echinococcus* spp.), hookworms (*Ancylostoma* spp., *Cyathostoma* spp.), roundworms (*Toxocara canis*, *Toxascaris leonina*), and whipworms (*Trichostrongylus axei*) in dogs.

USE DIRECTIONS: 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 oral dose.

DOSEAGE CHARTS

Drontal® Plus Tablets for Puppies and Small Dogs* (2-25 lbs.)		Drontal® Plus Tablets for Medium Sized Dogs (26-50 lbs.)		Drontal® Plus Tablets for Large Dogs (51 lbs. and greater)	
Body Wt. (lbs.)	No. of Tablets	Body Wt. (lbs.)	No. of Tablets	Body Wt. (lbs.)	No. of Tablets
2 - 4	0.5	25 - 30	1.0	45 - 63	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.

ADMINISTRATION: Drontal® Plus Tablets have been developed for oral administration. Tablets may be given directly by mouth or placed in a small amount of food. Feeding is neither necessary nor recommended prior to or after treatment.

RESTRAINTS: For those animals living where mosquitoes are likely to occur, clients should be instructed in the steps to optimize prevention; otherwise, restraint may be necessary. This is true in cases of *Dipylidium caninum* where reinfestation by fleas, certain to occur if fleas are not removed from the animal and its environment. In addition, for control of *Echinococcus multilocularis*, a program of regular treatment every 21 to 28 days may be indicated (see *E. multilocularis* section below).

ECHINOCOCCUS MULTILOCULARIS: *Echinococcus multilocularis* is a tapeworm species usually found in wild canids, including foxes, coyotes and wolves. The parasite has also been identified in domestic dogs and cats and is potentially a serious public health concern because it may infect humans.

The life cycle of the parasite is based on a predator-prey relationship, as depicted below.



The adult tapeworm is small (1-4mm) and resides in the intestinal tract of the definitive host (wild or domestic canids). Eggs from the adult tapeworm are shed in the feces. Rodents such as mice and voles serve as the intermediate hosts. Eggs ingested by rodents develop in the liver, lungs and other organs to form multilocular cysts. The life cycle is completed when a canid consumes a rodent infected with cysts. Larvae within the cysts develop into adult tapeworms in the intestinal tract of the canid. Eggs may be passed in the feces of the canid approximately 28 days later.

This parasite poses a serious public health problem because of the possibility for human involvement in the life cycle. If eggs shed by an infested animal are accidentally ingested, a highly pathogenic condition (alveolar hydatid disease) results from development of the cyst stage in humans.

The original geographic distribution of *E. multilocularis* was primarily confined to northern areas of North America. Current evidence indicates migration of the parasite well into the continental United States.

Domestic dogs living in *E. multilocularis* endemic areas that roam freely with the opportunity to catch wild rodents are at risk of infection. Pet owners should be advised on how to minimize this risk. Proper restraint of dogs should be encouraged, along with regular treatment with Drontal® Plus Tablets, following the dosing schedule stated and precautions indicated below.

Additional information on the life cycle and epidemiology of this parasite is available in veterinary parasitology texts.

DIAGNOSIS: Diagnosis of *E. multilocularis* in canids is difficult. The adult tapeworm produces no clinical signs of infection. Tapeworm segments (proglottids) are usually not observed in the feces. *E. multilocularis* eggs, observed using microscopic fecal examination procedures, are similar in appearance to those of common species such as *Isospora* spp.

Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Tablets

Broad Spectrum Anthelmintic for Dogs

DESCRIPTION: Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Anthelmintic Tablets are available in three sizes. Each size is scored for convenient oral administration.

Each Drontal® Plus 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 Drontal® Plus Tablet for Medium Sized Dogs contains 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate and 340.2 mg febantel.

Each Drontal® Plus Tablet for Large Dogs contains 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate and 680.4 mg febantel.

ACTION: Drontal® Plus Tablets contain three active ingredients having different modes of action and spectra of activity. Praziquantel is active against cestodes (tapeworms). Praziquantel is absorbed, metabolized in the liver and excreted in the bile. Upon entering the digestive tract from the bile, cestode activity is inhibited. Following exposure to praziquantel, the tapeworm loses its ability to resist digestion by the mammalian host. Because of this, whole tapeworms, including the

scotiae, are very rarely passed after administration of praziquantel. In many instances only disintegrated and partially digested pieces of tapeworm will be seen in the stool. The majority of tapeworms are digested and are not found in the feces.

Pyrantel pamoate is active against hookworms and ascarids. Pyrantel pamoate acts on the cholinergic receptors of the nematode resulting in spastic paralysis. Peristaltic action of the intestinal tract then eliminates the parasite.¹

Febantel is active against nematode parasites including whipworms. Febantel is rapidly absorbed and metabolized in the animal. Available information suggests that the parasite's energy metabolism is blocked, leading to energy exchange breakdown and inhibited glucose uptake.

Laboratory efficacy and clinical studies conducted with Drontal® Plus Tablets demonstrate that each of the three active ingredients act independently without interference. The combined tablet formulation provides a wide spectrum of activity against the indicated species of intestinal helminths.

INDICATIONS: Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Anthelmintic Tablets are indicated for removal of tapeworms (*Dipylidium caninum*, *Taenia platensis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*). For removal of hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*), and Whipworms (*Trichouris vulpis*) in dogs.

USE DIRECTIONS
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 oral treatment.

DOSEAGE CHARTS

Drontal® Plus Tablets in Puppies and Small Dogs (22.7 mg)		Drontal® Plus Tablets in Medium Sized Dogs (68.0 mg)		Drontal® Plus Tablets in Large Dogs (136.0 mg)	
Tablets	Weight (kg)	Tablets	Weight (kg)	Tablets	Weight (kg)
2	4-11	1	11-25	2	25-45
3	12-15	2	26-45	3	46-75
4	16-25	3	46-75	4	76-113
5	26-45	4	76-113	5	114-151
6	46-75	5	114-151	6	152-227
7	76-113	6	152-227	7	228-340
8	114-151	7	228-340	8	341-453
9	152-227	8	341-453	9	454-680
10	228-340	9	454-680	10	681-1013
11	341-453	10	681-1013	11	1014-1513
12	454-680	11	1014-1513	12	1514-2273
13	681-1013	12	1514-2273	13	2274-3402
14	1014-1513	13	2274-3402	14	3403-5132
15	1514-2273	14	3403-5132	15	5133-7562
16	2274-3402	15	5133-7562	16	7563-11342
17	3403-5132	16	7563-11342	17	11343-17012
18	5133-7562	17	11343-17012	18	17013-25512
19	7563-11342	18	17013-25512	19	25513-38262
20	11343-17012	19	25513-38262	20	38263-57392
21	17013-25512	20	38263-57392	21	57393-86042
22	25513-38262	21	57393-86042	22	86043-129092
23	38263-57392	22	86043-129092	23	129093-193642
24	57393-86042	23	129093-193642	24	193643-289192
25	86043-129092	24	193643-289192	25	289193-438742
26	129093-193642	25	289193-438742	26	438743-665292
27	193643-289192	26	438743-665292	27	665293-1000842
28	289193-438742	27	665293-1000842	28	1000843-1501392
29	438743-665292	28	1000843-1501392	29	1501393-2252042
30	665293-1000842	29	1501393-2252042	30	2252043-3427692
31	1000843-1501392	30	2252043-3427692	31	3427693-5183342
32	1501393-2252042	31	3427693-5183342	32	5183343-7739092
33	2252043-3427692	32	5183343-7739092	33	7739093-11694742
34	3427693-5183342	33	7739093-11694742	34	11694743-17650492
35	5183343-7739092	34	11694743-17650492	35	17650493-26706242
36	7739093-11694742	35	17650493-26706242	36	26706243-40061992
37	11694743-17650492	36	26706243-40061992	37	40061993-59717742
38	17650493-26706242	37	40061993-59717742	38	59717743-88373492
39	26706243-40061992	38	59717743-88373492	39	88373493-132929992
40	40061993-59717742	39	88373493-132929992	40	132929993-200486492
41	59717743-88373492	40	132929993-200486492	41	200486493-299042992
42	88373493-132929992	41	200486493-299042992	42	299042993-448599492
43	132929993-200486492	42	299042993-448599492	43	448599493-674155992
44	200486493-299042992	43	448599493-674155992	44	674155993-1019711992
45	299042993-448599492	44	674155993-1019711992	45	1019711993-1535267992
46	448599493-674155992	45	1019711993-1535267992	46	1535267993-2300822992
47	674155993-1019711992	46	1535267993-2300822992	47	2300822993-3436377992
48	1019711993-1535267992	47	2300822993-3436377992	48	3436377993-5141932992
49	1535267993-2300822992	48	3436377993-5141932992	49	5141932993-7617487992
50	2300822993-3436377992	49	5141932993-7617487992	50	7617487993-11273037992
51	3436377993-5141932992	50	7617487993-11273037992	51	11273037993-16828587992
52	5141932993-7617487992	51	11273037993-16828587992	52	16828587993-25384137992
53	7617487993-11273037992	52	16828587993-25384137992	53	25384137993-38039687992
54	11273037993-16828587992	53	25384137993-38039687992	54	38039687993-56695237992
55	16828587993-25384137992	54	38039687993-56695237992	55	56695237993-84350787992
56	25384137993-38039687992	55	56695237993-84350787992	56	84350787993-125906287992
57	38039687993-56695237992	56	84350787993-125906287992	57	125906287993-187461787992
58	56695237993-84350787992	57	125906287993-187461787992	58	187461787993-279017287992
59	84350787993-125906287992	58	187461787993-279017287992	59	279017287993-415572787992
60	125906287993-187461787992	59	279017287993-415572787992	60	415572787993-621128287992
61	187461787993-279017287992	60	415572787993-621128287992	61	621128287993-916683787992
62	279017287993-415572787992	61	621128287993-916683787992	62	916683787993-1362238787992
63	415572787993-621128287992	62	916683787993-1362238787992	63	1362238787993-2037793787992
64	621128287993-916683787992	63	1362238787993-2037793787992	64	2037793787993-3013348787992
65	916683787993-1362238787992	64	2037793787993-3013348787992	65	3013348787993-4478903787992
66	1362238787993-2037793787992	65	3013348787993-4478903787992	66	4478903787993-6734458787992
67	2037793787993-3013348787992	66	4478903787993-6734458787992	67	6734458787993-10090008787992
68	3013348787993-4478903787992	67	6734458787993-10090008787992	68	10090008787993-15045558787992
69	4478903787993-6734458787992	68	10090008787993-15045558787992	69	15045558787993-22401108787992
70	6734458787993-10090008787992	69	15045558787993-22401108787992	70	22401108787993-33956658787992
71	10090008787993-15045558787992	70	22401108787993-33956658787992	71	33956658787993-51412208787992
72	15045558787993-22401108787992	71	33956658787993-51412208787992	72	51412208787993-76967758787992
73	22401108787993-33956658787992	72	51412208787993-76967758787992	73	76967758787993-114523258787992
74	33956658787993-51412208787992	73	76967758787993-114523258787992	74	114523258787993-173078758787992
75	51412208787993-76967758787992	74	114523258787993-173078758787992	75	173078758787993-259634258787992
76	76967758787993-114523258787992	75	173078758787993-259634258787992	76	259634258787993-390189758787992
77	114523258787993-173078758787992	76	259634258787993-390189758787992	77	390189758787993-575745258787992
78	173078758787993-259634258787992	77	390189758787993-575745258787992	78	575745258787993-856300758787992
79	259634258787993-390189758787992	78	575745258787993-856300758787992	79	856300758787993-1281855758787992
80	390189758787993-575745258787992	79	856300758787993-1281855758787992	80	1281855758787993-1917410758787992
81	575745258787993-856300758787992	80	1281855758787993-1917410758787992	81	1917410758787993-2842965758787992
82	856300758787993-1281855758787992	81	1917410758787993-2842965758787992	82	2842965758787993-4258520758787992
83	1281855758787993-1917410758787992	82	2842965758787993-4258520758787992	83	4258520758787993-6414075758787992
84	1917410758787993-2842965758787992	83	4258520758787993-6414075758787992	84	6414075758787993-9569630758787992
85	2842965758787993-4258520758787992	84	6414075758787993-9569630758787992	85	9569630758787993-14325180758787992
86	4258520758787993-6414075758787992	85	9569630758787993-14325180758787992	86	14325180758787993-21680730758787992
87	6414075758787993-9569630758787992	86	14325180758787993-21680730758787992	87	21680730758787993-32736280758787992
88	9569630758787993-14325180758787992	87	21680730758787993-32736280758787992	88	32736280758787993-49391830758787992
89	14325180758787993-21680730758787992	88	32736280758787993-49391830758787992	89	49391830758787993-73947380758787992
90	21680730758787993-32736280758787992	89	49391830758787993-73947380758787992	90	73947380758787993-110502880758787992
91	32736280758787993-49391830758787992	90	73947380758787993-110502880758787992	91	110502880758787993-166058380758787992
92	49391830758787993-73947380758787992	91	110502880758787993-166058380758787992	92	166058380758787993-249613880758787992
93	73947380758787993-110502880758787992	92	166058380758787993-249613880758787992	93	249613880758787993-371169380758787992
94	110502880758787993-166058380758787992	93	249613880758787993-371169380758787992	94	371169380758787993-554724880758787992
95	166058380758787993-249613880758787992	94	371169380758787993-554724880758787992	95	554724880758787993-830280380758787992
96	249613880758787993-371169380758787992	95	554724880758787993-830280380758787992	96	830280380758787993-1245835380758787992
97	371169380758787993-554724880758787992	96	830280380758787993-1245835380758787992	97	1245835380758787993-1871390380758787992
98	554724880758787993-8302803807587879				

41239

For removal of Tapeworms (*Ephyridium caninum*, *Therapsyllium granulosum*, and removal and control of *Echinococcus multilocularis*). For removal of Hookworms (*Uncinostenoxyuris caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*) and Whipworms (*Trichostrongylus axei*) in dogs. **DO NOT USE IN PREGNANT ANIMALS.** Administer the proper dose as specified in the following table as a single oral treatment.

Body Weight (lb.)	Number of Tablets
2-4	0.5
5-7	1.0
8-10	1.5
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.** Tablets may be given directly by mouth or dissolved in a small amount of food. Fasten to further necessary for recommended prior to or after treatment. **CONTRAINDICATIONS:** DO NOT USE IN PREGNANT ANIMALS. Consult package insert for further details. 08713130-177099 08714827-7107880, R/L



ABTU

TREATMENT: Dogs infected with *E. multilocularis* should be treated to prevent exposure of humans to infective eggs and to break the parasite's life cycle.

The dosage of Droncit® Plus Tablets for removal of *E. multilocularis* is the same as that indicated for the removal of the other tapeworm species listed on the label. Laboratory efficacy studies have demonstrated the recommended dosage is 100% effective.

Under condition of continual exposure to wild rodents, retreatment of the dog at 21-28 day intervals is recommended to prevent the shedding of infectious eggs.

PRECAUTIONS: Strict hygienic precautions should be taken when handling dogs or feces suspected of harboring *E. multilocularis*. Infected dogs treated for the

first time with Droncit® Plus Tablets and dogs treated at intervals greater than 28 days may shed eggs in the feces after treatment. The animal should be held in the clinic during this interval and all feces should be incinerated or autoclaved. If these procedures are not possible, the eggs can be destroyed by soaking the feces in a sodium hypochlorite (bleach) solution of 3.75% or greater.* All areas where the animal was restrained or in contact with should be thoroughly cleaned with sodium hypochlorite and allowed to dry completely before reuse.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Dogs treated with elevated levels (5 consecutive days with 3 times the labeled dosage rate) of the combination of febantel and praziquantel in early pregnancy demonstrated an increased incidence of abortion and fetal abnormalities.† The effects of Droncit® Plus on pregnant animals have

not been determined.

There are no known contraindications against the use of praziquantel or pyrantel pamoate in dogs.

EFFICACY: A total of 178 dogs and puppies with naturally acquired or experimental parasite infections were included in 4 well-controlled laboratory studies to establish the efficacy of Droncit® Plus Tablets. In addition, 133 dogs and puppies were included in clinical field studies conducted in 5 veterinary clinics at different geographic locations throughout the United States to further evaluate safety and efficacy. These studies included dogs of various sizes, ages and breeds. Data from these studies demonstrated Droncit® Plus Tablets are safe and efficacious for the removal of the parasite species indicated on the label when used as directed.

STORAGE CONDITIONS: Droncit® Plus Tablets should be stored at controlled room temperatures between 59-86°F (15-30°C).

HOW SUPPLIED: Each tablet also is available in bottles of 50 (puppies and small dogs, medium sized dogs) or 30 (large dogs). Code 08713130-176099 50 Tablets/Bottle (Puppies and Small Dogs) Code 08713149-177099 50 Tablets/Bottle (Medium Sized Dogs) Code 08724639 30 Tablets/Bottle (Large Dogs)

REFERENCES:

- * Andrews, P., 1978. Pharmacokinetic Studies with DRONCIT® in Animals. Using a Biological Assay. *Veterinary Medical Review*, 2:154-165.
† Campbell, W.C., 1986. The Chemotherapy of Parasitic Infections. *J. Parasit.* 72(1):45-61; Hildreth, M.B., Johnson, M.D.

and Kazacos, K.R., 1991. A Zoonosis of Increasing Concern in the United States. *Compendium for Cont. Ed.* 13(5): 727-740.

* Lieby, P.D., Carney, W.P., and Woods, C.E., 1970. Studies on Syvatic Echinococcosis. II. Host Occurrence and Geographic Distribution of *Echinococcus multilocularis* in the North Central United States. *J. Parasit.* 56(5): 1141-1150.

* Georgi, J. R. and Georgi, M.E., 1980. *Parasitology for Veterinarians*. W.B. Saunders Co. 118-138.

* Soelby, E.J.L., 1982. *Helmintic Antiparasitics and Protozoa of Domesticated Animals*. 7th Edition. Lea & Febiger, 118-138.
* Craig, P.S. and McPherson, C.N.L., 1988. Sodium Hypochlorite as an Oxidant for Echinococcosis. *Ann Trop Med and Parasit.* 82(2): 211-213.

Results obtained in the laboratory and clinical studies indicate small numbers of hookworm or 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 to 4 weeks after treatment to determine the need for retreatment.

SIDE EFFECTS: None of the 103 dogs treated with Droncit® Plus Anthelmintic Tablets in the clinical field studies exhibited drug related side effects.

ANIMAL TOXICOLOGY: Controlled safety evaluations have been conducted in dogs with Droncit® Plus (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Anthelmintic Tablets. Dogs receiving up to 5 times the label dosage (35 mg praziquantel, 35 mg pyrantel pamoate and 179 mg febantel per kg of body weight) for 3 consecutive days (3 times the label dura-

tion) showed clinical signs of vomiting and non-formed stools. One dog receiving a 3 times labeled dose had elevated SGPT, SCOT, CPK and GOT readings (outside of normal range) at 6 days post-treatment. No additional findings were noted in hematological/clinical chemistry parameters nor were there any treatment related histological lesions. Vomiting was the only side effect observed when dogs received a single treatment of 61 mg praziquantel, 61 mg pyrantel pamoate and 305 mg febantel with one dog having an elevated SGPT reading (outside of normal range) at 24 hours post-treatment which had returned to normal by 7 days.

WARNING: KEEP OUT OF REACH OF CHILDREN.

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

* Freedom of Information Summary (FOI) NADA 133-653 (Febantel Pamoate Tablets)

October, 2002

Bayer

Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-007, Approved by FDA

Medium
Dog
Insert

Drontal® Plus (praziquantel/pyrantel pamoate/fabotol) Tablets

Broad Spectrum Anthelmintic for Dogs

DESCRIPTION: Drontal® Plus (praziquantel/pyrantel pamoate/fabotol) Broad Spectrum Anthelmintic Tablets are available in three sizes. Each size is scored for convenient oral administration.

Each Drontal® Plus Tablet for Puppies and Small Dogs contains 22.7 mg praziquantel, 22.1 mg pyrantel base as pyrantel pamoate and 113.4 mg fabotol.

Each Drontal® Plus Tablet for Medium Sized Dogs contains 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate and 340.2 mg fabotol.

Each Drontal® Plus Tablet for Large Dogs contains 135.0 mg praziquantel, 135.0 mg pyrantel base as pyrantel pamoate, and 680.4 mg fabotol.

ACTION: Drontal® Plus Tablets contain three active ingredients having different modes of action and spectra of activity. Praziquantel is active against cestodes (tapeworms). Praziquantel is absorbed, metabolized in the liver and excreted in the bile. Upon entering the digestive tract from the bile, cestocidal activity is exhibited. Following exposure to praziquantel, the tapeworm loses its ability to resist digestion by the mammalian host. Because of this, whole tapeworms, including the scoleces, are very rarely passed after administration of praziquantel. In many instances only digested and partially digested pieces of tapeworms will be seen in the stool. The majority of tapeworms are digested and are not found in the feces.

Pyrantel pamoate is active against hookworms and ascarids. Pyrantel pamoate acts on the cholinergic receptors of the nematode resulting in spastic paralysis. Paralytic action of the intestinal tract then eliminates the parasite.

Fabotol is active against nematode parasites including whipworms. Fabotol is rapidly absorbed and metabolized in the animal. Available information suggests that the parasite's energy metabolism is blocked, leading to energy exhaustion and inhibited glucose uptake. Laboratory efficacy and clinical studies conducted with Drontal® Plus Tablets demonstrate that each of the three active ingredients act independently without interference. The combined label formulation provides a wide spectrum of activity against the indicated species of intestinal nematodes.

INDICATIONS: Drontal® Plus (praziquantel/pyrantel pamoate/fabotol) Broad Spectrum Anthelmintic Tablets are indicated for removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*). For removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*), and Whipworms (*Trichouris vulpis*) in dogs.

USE DIRECTIONS

DOSEAGE: 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 oral treatment.

DOSEAGE CHARTS

Drontal® Plus Tablets for Puppies and Small Dogs (2-25 lbs.)		Drontal® Plus Tablets for Medium Sized Dogs (25-60 lbs.)		Drontal® Plus Tablets for Large Dogs (60 lbs. and greater)	
Body Wt. (lb.)	No. of Tablets	Body Wt. (lb.)	No. of Tablets	Body Wt. (lb.)	No. of Tablets
2 - 4	1/2	25 - 30	1	60 - 80	1 1/2
5 - 7	1/2	31 - 40	1	81 - 110	1 1/2
8 - 12	1	41 - 50	1 1/2	111 - 150	2
13 - 18	1	51 - 60	2	151 - 200	2 1/2
19 - 25	1 1/2	61 - 70	2 1/2	201 - 250	3

*NOT FOR USE IN PUPPIES LESS THAN 3 WEEKS OF AGE OR DOGS WEIGHING LESS THAN 12 LBS.

ADMINISTRATION: Drontal® Plus Tablets have been developed for oral administration. 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.

RETREATMENT: For those animals living where reinfestations are likely to occur, clients should be instructed in the steps to optimize prevention. Otherwise, retreatment may be necessary. This is true in cases of *Dipylidium caninum* where reinfestation is almost certain to occur if fleas are not removed from the animal and its environment. In addition, for control of *Echinococcus multilocularis*, a program of regular treatment every 21 to 26 days may be indicated (see *E. multilocularis* section below).

ECHINOCOCCUS MULTILOCULARIS: *Echinococcus multilocularis* is a tapeworm species usually found in wild canids, including foxes, coyotes and wolves. The parasite has also been identified in domestic dogs and cats and is potentially a serious public health concern because it may infect humans.



The life cycle of the parasite is based on a predator-prey relationship, as depicted above.

The adult tapeworm is small (1-4 mm) and resides in the intestinal tract of the definitive host (wild or domestic canids). Eggs from the adult tapeworm are shed in the feces. Rodents such as mice and voles serve as the intermediate host. Eggs ingested by rodents develop in the liver, lungs and other organs to form multilocular cysts. The life cycle is completed after a canid consumes a rodent infested with cysts. Larvae within the cysts develop into adult tapeworms in the intestinal tract of the canid. Eggs may be passed in the feces of the canid approximately 28 days later.

This parasite poses a serious public health problem because of the possibility for human involvement in the life cycle. If eggs shed by an infested canid are accidentally ingested, a highly pathogenic condition (Alveolar Hydatid Disease) results from development of the cyst stage in humans.

The original geographic distribution of *E. multilocularis* is primarily confined to northern areas of North America. Current evidence indicates migration of the parasite well into the continental United States.

Domestic dogs living in *E. multilocularis* endemic areas are at risk of infection. Pet owners should be advised on how to minimize this risk. Proper restraint of dogs should be encouraged, along with regular treatment with Drontal® Plus Tablets, following the dosing schedule aforementioned and precautions indicated below.

Additional information on the life cycle and epidemiology of this parasite is available in veterinary parasitology texts.

DIAGNOSIS: Diagnosis of *E. multilocularis* in canids is difficult. The adult tapeworm produces no clinical signs of infection. Tapeworm segments (proglottids) are usually not observed in the feces. *E. multilocularis* eggs, observed using microscopic fecal examination procedures, are similar in appearance to those of common species such as *Taenia pisiformis*.

Assistance in the diagnosis of *E. multilocularis* may be available from a state veterinary diagnostic laboratory.

Additional information regarding areas where *E. multilocularis* is suspected or has been confirmed may be obtained from area veterinary schools or the Centers for Disease Control in Atlanta, GA.

TREATMENT: Dogs infected with *E. multilocularis* should be treated to prevent exposure of humans to infective eggs and to break the parasite's life cycle.

The dosage of Drontal® Plus Tablets for removal of *E. multilocularis* is the same as that indicated for the removal of the other tapeworm species listed on the label. Laboratory efficacy studies have demonstrated the recommended dosage is 100% effective.

Under condition of continual exposure to wild rodents, retreatment of the dog at 21-26 day intervals is recommended to prevent the shedding of infectious eggs.

PRECAUTIONS: Strict hygienic precautions should be taken when handling dogs or feces suspected of harboring *E. multilocularis*. Infected dogs treated for the first time with Drontal® Plus Tablets and dogs treated at least more than 28 days may shed eggs in the feces after treatment. The animal should be held in the clinic during the interval and all feces should be incinerated or autoclaved. If these procedures are not possible, the eggs can be destroyed by soaking the feces in sodium hypochlorite (bleach) solution of 3.75% or greater. All areas where the animal was maintained or in contact with should be thoroughly cleaned with sodium hypochlorite and allowed to dry completely before reuse.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Dogs treated with elevated levels (5 consecutive days with 3 times the labeled dosage rate) of the combination of fabotol and praziquantel in early pregnancy demonstrated an increased incidence of fetal resorptions and fetal abnormalities. The effects of Drontal® Plus on pregnant animals have not been determined.

There are no known contraindications against the use of praziquantel or pyrantel pamoate in dogs.

EFFICACY: A total of 176 dogs and puppies with naturally acquired or experimental parasite infections 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 5 veterinary clinics at different geographic locations throughout the United States to further evaluate safety and efficacy. These studies included dogs of various ages, ages and breeds. Data from 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 or 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 7 to 14 days after treatment to determine its need for retreatment.

SIDE EFFECTS: None of the 103 dogs treated with Drontal® Plus Anthelmintic Tablets in the clinical field studies exhibited drug related side effects.

ANIMAL TOXICOLOGY: Controlled safety evaluations have been conducted in dogs with Drontal® Plus (praziquantel/pyrantel pamoate/fabotol) Broad Spectrum Anthelmintic Tablets. Dogs receiving up to 5 times the label dosage (55 mg praziquantel, 55 mg pyrantel pamoate and 179 mg fabotol per lb of body weight) for 3 consecutive days (3 times the label duration) showed clinical signs of vomiting and non-furred stools. One dog receiving 3 times labeled dose had elevated SGPT, SGOT, CPK and GGT readings (outside of normal range) at 8 days post-treatment. No additional findings were noted in hematological/clinical chemistry parameters nor were there any treatment related histological lesions. Vomiting was the only side effect observed when dogs received a 5 times treatment of 19 mg praziquantel, 19 mg pyrantel pamoate and 305 mg fabotol/kg of one dog having an elevated SGPT reading (outside of normal range) at 24 hours post-treatment which had returned to normal by 7 days.

WARNING: KEEP OUT OF REACH OF CHILDREN.

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

STORAGE CONDITIONS: Drontal® Plus Tablets should be stored in controlled room temperatures between 59-86°F (15-30°F).

HOW SUPPLIED: Each tablet size is available in bottles of 50 (puppies and small dogs), medium sized dogs or 30 (large dogs).

Code 08713150-17609 50 Tablets/Bottle (Puppies and Small Dogs)
Code 08713149-17709 50 Tablets/Bottle (Medium Sized Dog)

Code 08724639 30 Tablets/Bottle (Large Dog)

REFERENCES:

- Andrews, P., 1976. Pharmacological Studies with DRONTAL® in Animals Using a Biological Assay. *Veterinary Medicine* 71:134-136.
- Campbell, W.C., 1968. The Chemotherapy of Parasitic Infections. J. Parasit. 72(1):46-61.
- Hansen, M.B., Johnson, M.D. and Kazacos, K.R., 1991. A Zoonosis of Increasing Concern in the United States. *Compendium for Cont. Ed.* 13(5):727-740.
- Luby, P.D., Carney, J.P. and Wood, C.S., 1970. Studies on Syntactic *Echinococcus*. II. Host Occurrence and Geographic Distribution of *Echinococcus multilocularis* in the North Central United States. *J. Parasit.* 56(6):1141-1150.
- George, J.R. and George, M.E., 1990. *Parasitology for Veterinarians*. W.B. Saunders Co. 118-138.
- Scutney, E.J.L., 1982. *Helminths, Arthropods and Protozoa of Domesticated Animals*. 7th Edition. Lea & Febiger. 115-138.
- Craig, P.S. and McPherson, C.N.L., 1988. Sodium Hypochlorite as an Oxidant for *Echinococcus*. *Ann Trop Med. and Parasit.* 82(2):211-215.
- Freedom of Information Summary (F.O.I.) NADA 133-853 Vercom Paste (fabotol and praziquantel)

October, 2002 **Bayer**

Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-1007, Approved by FDA

228899 784

For removal of tapeworms (Dipylidium caninum, Taenia pisiformis, Echinococcus multilocularis). For removal of hookworms (Ancylostoma caninum, Uncinaria stenocephala) and whipworms (Trichouris vulpis) in dogs. Do not use in cats. Do not use in puppies less than 3 weeks of age. Do not use in pregnant animals. Tablets are scored for convenient oral administration.

Body Weight (lb.)	Number of Tablets
2 - 4	1/2
5 - 7	1/2
8 - 12	1
13 - 18	1
19 - 25	1 1/2
26 - 30	1
31 - 40	1
41 - 50	1 1/2
51 - 60	2
61 - 70	2 1/2
71 - 80	3

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.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS.

Control package insert for further details.

08713150-17709 R6

▲ OPEN ALONG PERFORATION ▲