Approval Date: May 25, 1984

I. GENERAL INFORMATION

A. File Number

NADA 101-331

B. Sponsor

Ralston Purina Company
Checkerboard Square
St. Louis, MO 63188

C. Proprietary Name

Dog Wormer Tablets

D. Established Name

Pyrantel pamoate

E. Dosage Form

Purina Dog Wormer Tablets are formulated in three sizes of oral tablets at concentrations of 22.7 mg., 45.4 mg. and 113.5 mg. pyrantel base aspyrantel pamoate per tablet.

F. Dispensing Status

OTC

G. Recommended Dosages:

22.7 mg pyrantel base as pyrantel pamoate tablet - 1 tablet per each 10 lbs of dog body weight for dogs weighing over 5 lbs. and 1 tablet for dogs weighing less than 5 lbs. 45.4 mg pyrantel base as pyrantel pamoate tablet - 1 tablet per 20 lbs of dog body weight. Tablet may be broken in half to provide 1/2 tablet for 10 lbs body weight.

113.5 mg pyrantel base as pyrantel pamoate tablet - 1 tablet per 50 lbs of dog body weight. Tablet may be broken in half to provide 1/2 tablet for 25 lbs of body weight.

Label directions are designed to provide a minimum of 2.27 mg pyrantel base per pound body weight for dogs weighing more than 5 pounds body weight, and 4.54 mg pyrantel base per pound body weight for dogs weighing 5 lbs or less.

Tablets are scored to facilitate breaking of tablet for more accurate dosage.

Since anthelmintics cannot be relied upon to prevent reinfection or to remove larvae not present in the intestinal tract at the time of initial treatment, for maximum control, it is recommended that puppies be treated at 2, 3, 4, 6, 8 and 10 weeks of age. Lactating bitches should be treated 2-3 weeks after whelping. Adult dogs should be treated at monthly intervals to protect against environmental *T. canis* reinfection. Retreatment of adult dogs may be necessary at monthly

intervals as determined by laboratory fecal examinations or in animals kept in known contaminated quarters.

H. Route of Administration

Pyrantel pamoate oral tablets are administered orally by placing the tablet in a small amount of meat to be hand fed to the dog or by placing the tablets directly into the back of the dog's mouth.

I. Indication

For the control of roundworms (ascarids), *Toxocara canis*, repeat treatment is recommended in puppies, lactating bitches and adult dogs.

The claim(s) for the removal of roundworms (*Toxocara canis* and *Toxascaris leonina*) and hookworms (*Ancylostoma caninum* and *Uncinaria stenocephala*) in dogs and puppies was originally approved on November 14, 1978, based on the firm's data and cross-reference to Pfizer, Inc's., safety and efficacy data.

The presence of the above parasites should be confirmed by laboratory fecal examination. Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

J. Effect of Supplement

Will provide for repeat treatment of puppies, lactating bitches and adult dogs for control of *T. canis*.

II. EFFECTIVENESS

The effectiveness of Purina Dog Wormer Tablets has been established by data contained in approved NADA 101-331 (see attached Freedom of Information Summary for Pyrantel Pamoate Tablets for Dogs). This supplemental application demonstrates a need for repeat dosage and that Purina Dog Wormer Tablets continues to be effective when administered under repeat dosage conditions.

A. Literature References (establishing need for repeat dosage).

Pyrantel Pamoate can be a very valuable tool in reducing *T. canis* infection in dogs. Literature references support anthelmintic treatment and, specifically, Pyrantel Pamoate efficacy, [(1),(2),(3)]

(1) Beaver P.C. (1969) The Nature of Visceral Larval Migrans J. of Parasitol. 55 No. 1, Feb. 1969 p. 3-12

(2) Herd R. {1979) Preventing Visceral Larva Migrans JAVMA, Vol. 174, April'15, 1979 No. 8 p. 780-782

(3) Cypess R. H. (1978) Preventing Visceral Larva Migrans Cornell Veterinarian, 68, p. 283-296.

as does efficacy data contained in NADA 101-331.

To reduce or eliminate *T. canis* infection, repeated dosage of an effective anthelmintic is necessary to prevent reinfection. To determine the appropriate dosage intervals, understanding of *T. canis* life cycle is necessary. It follows the classic pattern of arrested development of larvae in the dog's somatic tissues. Not all larvae that hatch from eggs in dogs over one month of age reach maturity, but they encyst in the somatic tissues as second stage larvae. Routes of Migration include:

1. Puppy infection is primarily by migration of the second stage larvae from the somatic tissues of the bitch through the placenta to the developing pup. The third stage larvae is in the liver of the fetus and at whelping these larvae migrate to the lungs and from fourth stage larvae. Fourth stage larvae are coughed up, swallowed, and moult to the fifth stage in the intestine.

Fifth stage larvae are present in the two-week old puppy and mature to egg laying adults 3 weeks post-whelping.[(4),(5),(6)]

(4) Sprent, J.F.A. 1954 The life cycles of Nematodes in the Family Ascarididae Blachard 1896. J. Parasit. 40: 608-617 (copy not attached)

(5) Soulsby, E.J.L. Helminths, Arthropods and Protozoa of Domesticated Animals, Sixth Addition, 1968, The Williams and Wilkins Co., Baltimore, p. 160 {copy not attached)

(6) Douglas J.R. and Baker N.F. (1959) Chronology of Experimental Intrauterine infections with *Toxocara canis* (Werner, 1782) in the Dog. J. of Parasitol. Vol. 45, August 1959, p. 43-44.

2. In pups younger than one month, "tracheal" infections may occur. That is: hatched larvae migrate from the intestine - to the liver - to the lung and return to the intestine as adults. These infections originate from eggs picked up in the young pup's environment. (7) Recent research indicates all age dogs may be infected by this route depending on the number of infective eggs in the inoculum. (8)

(7) Sprent, J.F.A. 1958 0bservations on the Development of *Toxocara canis* (Werner, 1782) in the Dog. Parasitology 48: 184-209

(8) Dubey, J.P. 1978 Patent *Toxocara canis* Infection in Ascarid-Naive Dogs. J. Parasitol 64 (6) 1978 pp 1021-1023.

3. Patent infections are frequently observed in nursing bitches during the month following whelping. These infections are probably obtained by the bitch through third stage larvae which have failed to establish themselves in the pup's intestine and pass out in the feces. The bitch consumes these larvae through preening the anal regions of the pups. Since these larvae have already progressed through the third moult, they pass directly to the intestine to mature. (9)

(9) Sprent, J.F.A. (1961) Post-Parturient Infection of Bitch with *Toxocara canis*. J. of Parasitol, Vol. 47, No. 2, p. 284

4. Dogs over one month of age can acquire patent infections by. eating small animal carcasses, such as mice, rats, rabbits, or birds which contain encysted

second stage larvae. These larvae then mature through "tracheal" infections. [(7),(1)]

5. Dogs of all ages are susceptible to reinfection by *T. canis* from various means depending upon their age. An effective *T. canis* thelmintic program must disrupt all routes of infection. Since the prevalence of somatic larvae is so uniform in the bitch and can last through several pregnancies, it is imperative that all pups be treated. [(5),(10)] The puppy should be treated at 2, 3, 4, 6, 8, and 10. weeks of age to remove intestinal infections which are maturing either from placental origin or from fecal contamination of the pup's environment.

(10) Scothorn, M.W., F.R. Koutz, and H. F. Groves. (1965) Prenatal *Toxocara canis* Infections in Pups. JAVMA 146: 45-48

The lactating bitch should be treated at 2 to 3 weeks following whelping to prevent reinfection from third stage larvae.

To prevent adult dog reinfection monthly treatments are necessary because of their contact with paratenic hosts (rats, mice, rabbits, etc.). Human health is further protected by reducing *T. canis* contamination of our environment.

B. Critical Study (anthelmintics)

1. In compliance with 21 CFR 514.111{a)(5){vi) for controlled studies, the following adequate and well-controlled critical evaluations were conducted with the marketed product.

2. Name and address of investigator who did the study:

   Mr. C. W. Dickerson
   Health Industries Research Center
   Gray Summit, MO

3. General design of the investigation

   a. Purpose of study: To demonstrate that repeated dosage of pyrantel pamoate according to body weight as stated on label at 2, 3, 4, 6, 8 and 10 weeks of age will prevent the maturation of *T. canis* in dogs.
   b. Test animals:
      Mix breed dogs, 4 bitchs, produced 25 puppies for three test groups.

      Multidose - 9 puppies
      Single Dose - 10 puppies
      Control - 6 puppies

   c. Each bitch was orally intubated with *T. canis* eggs prior to pregnancy. Two pups from each litter were left untreated as a source of reinfection for the treated and control groups. The remaining pups from each litter were allotted to a multidose and a single dose group.
   d. Diagnosis: All test animals were euthanized, necropsied, and examined for parasites. Starting with the first week of life and weekly thereafter, fecal samples were collected for parasite egg identification.

e. Dosage Form: Single tablets currently manufactured and marketed in accordance with approved NADA 101-331.
f. Route of Administration: Oral
g. Dosage(s) Used: In accordance with label directions shown in part 3 of this summary.
h. Test Duration: 11 weeks. All animals were examined daily for physical appearance, signs of side effects or toxicity. Fecal parasite egg identification and gastrointestinal tract examination and parasite identification and counts as to genus, species, sex, and approximate maturity.

4. Results: PERCENT REDUCTION OF *TOXOCARA CANIS*

Treatment Group	Average of Worms/Pup at Necropsy (males, females & Immature)	Percent Reduction
A - (Multidose)	0	100
B - (Single Dose)	41.7	25
C - (Control)	55.7	--

5. Statistical Analysis

Percent efficacy was determined by:

$$\%Efficacy = \frac{(No.\,parasites\,in\,control\,animals - No.\,parasites\,in\,treated\,animals)}{No.\,parasites\,in\,control\,animals} \times 100$$

6. Conclusion drawn from the study:

a. Oral inoculation of *T. canis* larvated eggs to the pregnant bitch resulted in transplacental infections in all 4 litters.
b. Treatment of 9 puppies from 4 litters at 2, 3, 4, 6, 8 and 10 weeks of age with Purina Dog Wormer Tablets resulted in complete freedom of adult *T. canis* worms at necropsy.
c. Treatment of 10 puppies from 4 litters at 2 weeks of age resulted in 8 patent infections of *T. canis* at necropsy on the eleventh weeks. Adult worms were reduced 25% compared to control pups which did not receive any anthelmintic.
d. Six untreated puppies from 4 litters resulted in 6 patent infections of *T. canis* at necropsy on the eleventh week.

7. Adverse Reactions: None

C. Clinical (field) Study

1. Name and address of investigator who did the study:

Tom Amlung, D.V.M.
Belleville, IL

Charles Hertich, D.V.M.
Belleville, IL

Lance Allen, D.V.M.
Cedar Hill, MO

Ronald Ragan, D.V.M.
Cedar Hill, MO

Mitchel Oltman, D.V.M.
Arnold, MO

K. G. Silva, D.V.M.
Imperial, MO

W. N. Jones, D.V.M.
Florissant, MO

2. General design of the investigation:

e. Purpose:To demonstrate that repeat dosage of pyrantel pamoate according to label directions is safe and effective for prevention of maturation of *Toxocara canis* in dogs.
f. Test Animals:All varieties of dogs were used. Large, small, pure breed, mixed, male and female (total of 181 puppies). All puppies treated were under the care of a veterinarian. Natural infections of *Toxocara canis* in the bitch transferred infection.
g. Diagnosis:Fecal swabs or fecal samples were taken from each puppy at 4 weeks of age and checked for the presence of *Toxocara canis* eggs. If the samples were positive for *T. canis* the pups were re-sampled at 2 week intervals until their stool was negative for *T. canis* or at test termination.
h. Dosage Form:Tablets currently approved in accordance with NADA 101-331.
i. Route of Administration: Oral
j. Dosage Used: In accordance with label directions shown in part 3 of this summary.
k. Test Duration: 10 weeks
l. Pertinent Parameters Measured:Clinical signs and fecal egg counts for *T. canis*.

3. Results:181 puppies from 29 litters were on test. All puppies negative at 4 week except for 3 puppies which were negative at 6 weeks. No drug related side effects, toxicity or failure of the drug to perform were reported.

4. Statistical Analysis:Not applicable as this study was not designed to demonstrate critical efficacy.

5. Conclusion:Purina Dog Wormer Tablets are safe and effective for repeat dosage and the revised label directions should be approved.

6. Adverse Reactions: None

7. Special Issues: None

III. TARGET ANIMAL SAFETY

Animal safety of pyrantel pamoate oral dosage forms has been adequately demonstrated per Pfizer, Inc. approved NADA 100-237. Pfizer, Inc. provided authorization to Ralston Purina Company on 5/20/75 to refer to safety contained in Pfizer, Inc. NADA's 91-739, 100-237 and 16-803 in support of NADA 101-331 on page 00035.

IV. HUMAN FOOD SAFETY

As labeled, the drug poses no hazard to human safety pertaining to drug residues, because it is labeled for use in dogs only.

Human Safety Relative to Possession, Handling and Administration:
The labeling contains adequate caution statement.

V. AGENCY CONCLUSIONS

Data submitted satisfy the requirements of Section 512 of the Act and demonstrate that Purina Dog Wormer Tablet (Pyrantel Pamoate), when used under its proposed conditions of use is safe and effective for the control of ascarids (*Toxocara canis*) in puppies, lactating bitches and adult dogs.

Under The Center for Veterinary Medicine's Supplemental approval policy (42 FR 64367; December 23, 1977), this is a Category II Supplemental approval which involves a change in the dosing schedule. The approval is solely based on the published literature and additional effectiveness studies and does not require reevaluation of safety data in the parent application.

VI. ATTACHMENTS

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.