Approval Date: July 16, 1993

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 111-798

B. Sponsor

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

C. Proprietary Name

Droncit® 34 mg Canine Tablets

D. Established Name

praziquantel

E. Dispensing Status

Rx

F. Dosage Regimen

The recommended dosage of praziquantel varies according to body weight. Smaller animals require a relatively larger dosage because of their higher metabolic rate. The optimum dosage for each individual animal will be achieved by using the following dosage schedule:

Dogs and Puppies*	**Tablets**
5 Lbs and Under	0.5 Tablet
6 - 10 Lbs	1 Tablet
11 – 15 Lbs	1.5 Tablets
16 – 30 Lbs	2 Tablets
31 – 45 Lbs	3 Tablets
46 – 60 Lbs	4 Tablets
Over 60 Lbs	5 Tablets Max

*Not intended for use in puppies less than 4 weeks of age.

G. Route of Administration

Droncit (praziquantel) Canine Cestocide Tablets may be administered directly per os or crumbled and mixed with the feed.

H. Indication

DOGS: For the removal of *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*.

I. Effect of Supplement

This Supplemental Application amends the NADA to provide for the use of Droncit Tablets against *Echinococcus multilocularis* in dogs. Droncit Tablets (NADA #111-798, 46 FR 60570 [December 11, 1981]) are currently approved for use in dogs and cats.

II. EFFECTIVENESS

A. Pivotal Studies

1. Cross-reference to the existing FOI Summary for Droncit Cestocide Tablets (NADA 111-798, 46 FR 60570 [December 11, 1981]).

   The original FOI summary contain the details of the dose titration, dose confirmation and clinical field studies which established the dose and effectiveness of those products in dogs (and cats). The laboratory studies demonstrated at the recommended dose a complete (100%) elimination of the various common cestode species claimed on the label. Clinical field studies likewise established the effectiveness of praziquantel against the cestodes.

B. Pivotal - Well-Controlled Laboratory Effectiveness Studies

1. Efficacy of Praziquantel (Droncit) Against *Echinococcus multilocularis* in Dogs - K.R. Kazacos, West Lafayette, IN

   A controlled anthelmintic trial was conducted on 24 dogs according to CVM's Canine/Feline Anthelmintic Guidelines. All were adults of various mixed breeds, equal sex, ranging from 29 to 50 lbs. (13.2 to 22.7 kg) body weight. The dogs were randomly divided into 3 groups of 12. Twelve dogs were dosed according to the approved label (range = 4.8-7.0 mg/kg body weight) with the marketed 34 mg tablets, given orally directly by mouth. The remaining 12 dogs were untreated controls. Blinding of those doing the evaluations was used to minimize any potential bias.

   The test animals, prior to treatment evaluation, were each experimentally infected with Echinococcus multilocularis. This was done by feeding each dog an estimated minimum of 100,000 protoscolices harvested from infected gerbils. Because of the risk of a potentially fatal infection to those conducting the study, dosing was accomplished at 21 days after administering the protoscolices and necropsy was at 28 days. Diagnosis was by postmortem counting of *E. multilocularis* parasites. Also, each dog was observed at least twice daily from infection through necropsy for any indication of abnormal reactions or side effects.

   All 12 control dogs were infected with an average of 41,492 adult *E. multilocularis*. By comparison, all treated dogs, 12 with tablets, were completely negative for *E. multilocularis* (and as well for other cestodes), i.e. 100% elimination. No adverse clinical signs or reactions related to either the experimental infection or praziquantel treatment were observed.

   Praziquantel was effective and safe in treating *E. multilocularis* infections in dogs.

2. Efficacy of Praziquantel (Droncit) Against Immature *Echinococcus multilocularis* Infections in Dogs - K.R. Kazacos, West Lafayette, IN

   This was an 8-dog controlled anthelmintic trial conducted according to CVM's Canine/Feline Anthelmintic Guidelines. All were adults of various mixed breeds, equal sex, ranging from 34 to 52 lbs. (15.4 to 23.6 kg). The dogs were randomly divided into 4 groups of 2 dogs. Groups 1 through 3 were evaluated at 1, 7 and 14 days after experimental inoculation with a minimum of 100,000 protoscolices per dog. Group 4, infected the same, was evaluated following parasite maturation, for egg shedding in the feces. Blinding of those doing the evaluations was used to minimize any potential bias.

   Treated dogs received the label recommended dose (range 5.0 - 5.8 mg/kg body weight) of the currently marketed Droncit formulation. They received an oral dose of the 34 mg canine tablets. The treated dogs were all compared with the same number of untreated controls. There was one exception in Group 4. The 2 control dogs were held, by design, after necropsy of the treated dogs. At the conclusion of the egg monitoring interval, following all egg count comparisons, those dogs were also treated. The purpose was to observe the impact of praziquantel on more mature infections.

   Evaluations in this study included the impact of praziquantel on immature and mature *E. multilocularis* infections. Groups 1 through 3 were compared with untreated controls for actual parasite counts. No parasite count comparisons were possible in Group 4, as all of these dogs were eventually treated with praziquantel after evaluation of patent infections and egg shedding patterns. All animals were observed at least twice daily from infection through necropsy for evidence of adverse effects or reactions.

   The untreated controls averaged 46,317 *E. multilocularis* per dog; all were infected. All treated dogs had no E. multilocularis at necropsy, i.e. 100% elimination. Treatment of mature infections produced a spike in egg counts that lasted for up to 60 hours depending on the dog's fecal habits. The peak counts in the treated dogs were many times less than the dog allowed to continue shedding without treatment. No adverse effects or reactions were observed.

   Praziquantel was effective and safe for the treatment of immature *E. multilocularis* infections in dogs.

C. Clinical Efficacy Trial

1. A Program to Reduce the Risk of Infection by *Echinococcus multilocularis*: The Use of Praziquantel to Control the Cestode in a Village in the Hyperendemic Region of Alaska - R.L. Rausch, J.F. Wilson and P.M. Schantz - Anchorage, AK

   St. Lawrence Island in Alaska was the site of a 10-year clinical anthelmintic evaluation of the marketed tablet formulation of praziquantel. No treatments were given for the first 3 years during which the population of the larval stage of *E. multilocularis* was monitored in voles captured from the town of Savoonga. An estimated 80-90 dogs from Savoonga were dosed on a monthly basis for 7 consecutive years following the initial monitoring. The dogs were Huskies and other miscellaneous breeds of both sexes including a wide range of ages and

weights. All dogs were dosed orally according to the established label recommendations.

This island is part of a hyperendemic region for *E. muItiIocularis*. The complete life cycle of the parasite occurs on the island. *E. multilocularis* is passed between the Northern Voles and both wild (e.g. foxes) and domestic (e.g. dogs) canids. Humans, through contact with the canid hosts, occasionally contract the disease. The purpose of the study was to monitor the infection rate of the parasite in the voles once yearly. Humans are an accidental host, taking the place of the vole.

Monitoring the impact of praziquantel through the vole infection rate was considered by the investigators as a good measure of the exposure rate encountered by humans. Voles from the town were considered as being exposed to praziquantel-treated canids. Those captured outside the town were controls as they were exposed, primarily, to feces from untreated canids. This was a practical method for evaluating clinical response in a natural clinical setting. Diagnosis, therefore, was based on positive identification of the parasite in voles.

Over the first 3 years with no treatment, 29% of the voles in Savoonga were identified with *E. multilocularis*.By the third year of praziquantel dosing, the vole infection rate in Savoonga had dropped to 1%. Over the 7-year period of dosing, the average reduction in the vole infection rate was 83%. This translates to a similar reduction in the risk of a human infection. There were no reported adverse effects identified by the investigators following praziquantel dosing.

Praziquantel was safe for repeat administration over an extended period of multiple dosing. The beneficial impact of treatment was clear. The drug was safe and effective in the treatment and control of natural *E. multilocularis* infections in a clinical setting.

D. Corroborative Studies (Published Articles/Abstracts)

1. Cross-reference to the existing FOI Summary for Vercom (febantel/praziquantel) Paste (NADA 133-953, 50 FR 19167 [May 7, 1985]).

   Laboratory and clinical data gathered by the sponsor confirms the activity of praziquantel against cestode parasites, i.e. 100% elimination.

2. Efficacy of Praziquantel Against Immature *Echinococcus multilocularis* in Dogs and Cats - F.L. Andersen, J.R. Crellin and D.D. Cox, Provo, UT

   This was a controlled anthelmintic study involving experimentally induced *E. multilocularis* infections derived from cystic material in cotton rats. The eighteen dogs were each equally divided between an unmedicated control group and a treated group, given an intramuscular dose of the injectable solution. The dogs consisted of purebred and mixed breeds of both sexes and different ages, ranging from 7 to 50 lbs. (3.2 to 22.7 kg) body weight.

   Diagnosis was based on the identification of the parasite during necropsy. Treatments were given 21 days after infection and necropsy of all animals was 28 days after infection.

At necropsy, all 9 control dogs were infected. All dogs treated with praziquantel were negative for *E. multilocularis*, i.e. 100% elimination. Signs of toxicosis were not observed in any animals.

The injectable formulation of praziquantel was effective and safe for the elimination of *E. multilocularis* in dogs.

3. Efficacy of a Combined Paste Formulation of Praziquantel/Febantel Against Immature *Echinococcus granulosus* and immature *Echinococcus multilocularis* - F.L. Andersen, J.A. Short and H.D. McCurdy, Provo, UT

   A controlled anthelmintic study was conducted on 12 dogs using experimentally induced infections of *E. multilocularis*.The dogs were of multiple breeds and ages, of both sexes, ranging from 19 to 62 lbs. (8.4 to 28.2 kg) body weight. The dogs were given 25,000 *E. multilocularis* protoscolices from cotton rats. The dogs were divided into two groups of six. All treated dogs were dosed orally for three consecutive days beginning on day 21 after infection according to the label recommended dosages using the formulation intended for market. All were necropsied 28 days after infection. Diagnosis was based on the identification of the *Echinococcus* spp. collected from the intestinal tract.

   All *E. multilocularis* infected controls were positive at necropsy for their respective parasite. All treated dogs with both *Echinococcus parasites* were negative, i.e. 100% elimination. No adverse side effects were reported from any of the treated animals. Praziquantel, combined with febantel in a paste formulation, was effective and safe when used for the elimination of *E. multilocularis* in dogs.

III. TARGET ANIMAL SAFETY

A. Pivotal Confirmation of Safety

1. Cross reference to the existing FOI Summary for Droncit Cestocide Tablets (NADA 111-798, 46 FR 60570 [December 11, 1981]).

   The original FOI summary details the safety evaluation conducted in support of the approval for this product. The safety data include both laboratory and clinical evaluations conducted in accordance with existing FDA guidelines and a wide margin of safety was demonstrated for the praziquantel formulation.

   The two laboratory effectiveness trials referenced above (IVB1 & 2), the 10 year clinical efficacy study, as summarized above, and the 11 years of marketing the products to date have confirmed the safety of this drug.

2. A Programme to Reduce the Risk of Infection by Echinococcus multilocularis:The Use of Praziquantel to Control the Cestode in a Village in the Hyperendemic Region of Alaska - R.L. Rausch, J.F. Wilson and P.M. Schantz, Anchorage, AK.

   This was a seven year study in which 80-90 dogs were dosed at the label recommended rate at 30 day intervals continuously. No adverse effects were reported by the investigators. Multiple dosing with praziquantel tablets over an extended time was safe for the treated animals.

IV. HUMAN FOOD SAFETY

A. Human Food Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for the approval of this supplemental NADA. The drug is labeled for use in dogs which are non-food animals.

B. Human Safety Relative to Possession, Handling and Administration

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

V. AGENCY CONCLUSIONS

The data in support of this supplemental NADA satisfy the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrate that Droncit® (praziquantel) 34 mg tablets, when used under the labeled conditions of use, are safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the additional claim to include the removal and control of *Echinococcus multilocularis.* The approval of this change has no adverse effect on the safety and effectiveness of the new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

For this supplement, the drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine when removal or control of *Echinococcus multilocularis* infection is indicated.

For new animal drugs for use in non food-producing animals, Section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, provides for a three year period of exclusivity for a supplemental application which contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the supplement and conducted or sponsored by the applicant. This supplemental NADA qualifies for such an exclusivity period (new claim only), which will expire three years from the date of this approval.

VI. ATTACHMENTS

1. The color graphics for Droncit® 34 mg tablets for dogs
2. Droncit 50 count tablet bottle label
3. Droncit 50 count tablet bottle Fix-A-Form insert
4. Droncit 150 count tablet bottle label
5. Droncit 150 count tablet bottle Fix-A-Form insert

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.