Approval Date: January 18, 1990

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 111-798

B. Sponsor

Mobay Corporation, Animal Health Division
P.O. Box 390
Shawnee, Kansas 66201

C. Proprietary Name

CUTTER Tape-Tabs

D. Established Name

Praziquantel

E. Dosage Form

Tablets

F. Dispensing Status

OTC

G. Route of Administration

Oral

H. Indication

Dogs: CUTTER Tape-Tabs (praziquantel) Tapeworm Tablets will remove the common tapeworms, *Dipylidium caninum* and *Taenia pisiformis*, from dogs and puppies.

Cats: CUTTER Tape-Tabs (praziquantel) Tapeworm Tablets will remove the common tapeworms, *Dipylidium caninum* and *Taenia taeniaeformis*, from cats and kittens.

I. Effect of Supplement

The purpose of the supplement is to provide for OTC marketing of praziquantel tablets for the indications listed below.

II. EFFECTIVENESS

Studies were conducted to determine the dosage and formulation of praziquantel which produced the most reliable results when used for the removal of tapeworms from dogs and cats.

Acceptable efficacy was established as 100% elimination of the tapeworm parasites in all animals dosed. Initial oral studies were done with a range of dosages, some as low as 0.5 mg/kg body weight. The results were not always reproducible. One study conducted by Dr. S.M. Kruckenberg, Manhattan, KS, also determined that small dogs (less than 25 lbs) required a larger mg/kg dosage. Dr. Kruckenberg than related the minimum effective dosage to the surface area of the animal utilizing a formula in which the body weight is raised to the three-quarter power and then multiplied by a constant. Utilizing this formula as a basis, the dosage schedule was then achieved. The schedule was produced in order to eliminate the need for the practicing veterinarian to use a fairly complicated mathematical formula to calculate the minimum effective dose for dogs which are at the lower end of the weight range, however, the safety evaluations, as discussed below, allow for this higher dosage.

Twenty-five separate well-controlled critical anthelmintic studies (which involves the sacrificing of animals and examination to determine the number of parasites in the intestinal tract) were conducted with the final tablet formulation. Investigators for these studies were Dr. M.L. Sharp, Vernon Texas; Dr. S.M. Kruckenberg, Manhattan, KS; Dr. A.C. Todd, Madison, WI; and Drs. D.D. Cox and R.G. Arther, Mobay Corporation, Animal Health Division, Shawnee, KS.

A summary table of the investigators' results appears below. Two hundred and ninety-two animals were studied; 157 (100 dogs and 57 cats) were treated with praziquantel tablets orally or in food and 135 (80 dogs and 55 cats) served as untreated controls. Both natural and experimental infections were studied with some animals being infected with two species of tapeworms. All dogs and cats treated according to the recommended dosage schedule, and some treated at less than the recommended dosage schedule, were cleared of their tapeworm infections. At the same time, the untreated control animals, confirmed as positive before treatment, maintained their tapeworm infections, with the exception of four dogs and one cat that lost their infections spontaneously. In these studies, praziquantel tablets were 100% effective in the treatment of tapeworm infections of dogs and cats due to *Taenia pisiformis* , *Taenia taeniaeformis* and *Dipylidium caninum*. Additionally praziquantel effectively (100%) eliminated experimental *T. taeniaeformis* infections as young as seven (7) days from cats.

(Eds. note: The following table consists of 4 columns.)

Summary of Preclinical Effectiveness Data for Praziquantel Tablets in Dogs.

%Efficacy Against Tapeworms.

Investigator/Location	**Treated Dogs**	***T. pisiformis***	***D. caninum***
M.L. Sharp Vernon, TX	4	Not Studied	100
S.M. Kruckenberg Manhattan, KS	24	100**	100
D.D. Cox/R.G. Arther Mobay Corporation Animal Health Div. Shawnee, KS	29*	100	100
TOTAL	27		

* One animal underdosed was not cleared of its infection.

** Includes cats with experimentally induced immature (7-day old) infections.

Field investigations of praziquantel tablets were conducted by 12 investigators geographically distributed as follows:

1. Dr. Donald E. Berdan, Wenatchee, Washington
2. Dr. Harold Brauetigam, Frankenmuth, Michigan
3. Dr. W.F. Braunschweig, San Rafael, California
4. Dr. S.F. Cheesman, Pine Bluff, Arkansas
5. Dr. John Durling, Fort Scott, Kansas
6. Dr. J.S. Elder, Youngstown, Ohio
7. Dr. Douglas R. Funk, Wenatchee, Washington
8. Dr. M.A. Groh, Blue Springs, Missouri
9. Dr. Robert Isenhart, Wenatchee, Washington
10. Dr. Larry E. Martin III, Turlock, California
11. Dr. E.E. Schobert, Tampa, Florida

12. Dr. H. Travasos, Abbeville, Louisiana
The field trials were well-controlled using bunamidine hydrochloride as the positive control drug. Overall, 279 dogs and 173 cats were studied, including a wide range of ages, breeds, and weights of both sexes. Praziquantel Tablets were administered to 218 dogs and 135 cats while 61 dogs and 38 cats were dosed with bunamidine hydrochloride. Dosing was administered according to label directions. The animals were observed for the presence of tapeworms proglottids 10-14 days post-treatment; any proglottid found was identified. Investigators were asked to evaluate praziquantel for ease of administration, efficacy and safety on a scale of excellent, good, fair and poor. Investigators rated efficacy in dogs as excellent to good in 97% of the cases in dogs and cats. These trials confirmed preclinical efficacy results and demonstrated that praziquantel tablets, when used according to label directions, did have the effect it purports in its labeling.

III. TARGET ANIMAL SAFETY

A. Preclinical Safety Evaluation

The preclinical safety evaluations for this praziquantel tablet formulation were conducted in the United States by or under the direction of Mobay Corporation, Animal Health Division.

Dogs

Dr. J.A. Shmidl of Shawnee, Kansas conducted a study consisting of treating six dogs orally with tablet doses of 12.5 mg/kg with no effect on pregnancy, lactation or 41-day old puppies.

Two *Dirofilaria immitis*-infected dogs received 26-27 mg/kg oral tablet treatment by Dr. R. Christie at Jackson, Mississippi with no effect on microfilariae or adult heartworms.

Dr. Shmidl concluded no clinical signs of toxicity following treatment of two dogs at 25 and 50 mg/kg with tablets.

Dr. Shmidl administered ten tablet treatments to one male dog at 12.5 mg/kg with no effects on reproduction. He sired four normal litters in four breeding attempts.

Dr. Shmidl administered two tablet treatments at 14-day intervals to eight dogs with either 100 or 200 mg/kg doses. Vomition was the only sign of toxicity. Body weights, clinical pathology and histopathology were also evaluated.

Nine dogs (male and female) received tablet treatments up to 26.8 mg/kg during critical stages of reproduction by Dr. M. Barth of Mt. Horeb, Wisconsin. No effects occurred on fertility, conception, fetal development or pregnancy.

Dr. Shmidl concluded that tablet treatment of five dogs with 2X labeled doses had no effect on cholinesterase and was compatible with the simultaneous use of carbamate compounds.

Four puppies (4 1/2 to 5 weeks of age) received two 5X tablet treatment at 14 day intervals by Dr. Shmidl. No effects were observed as to clinical signs, body weights, gross- or histopathology.

Dr. Shmidl treated eight dogs twice at 14 day intervals with 5X or 10X the labeled tablet dose. Their weight range was five to 95 lb and the dosage rate was up to 147.8 mg/kg. Vomiting and diarrhea were the only clinical signs with no significant effects on body temperature, cholinesterase values, body weights, clinical pathology or histopathology.

The tablet formulation has been administered to more than 4,480 dogs in foreign countries at doses of 10 mg/kg and up to the label dose at monthly intervals with no reported adverse reactions (Australia, South America and New Zealand).

Cats

Dr. J.A. Shmidl in Shawnee, Kansas treated two cats orally with doses of 25 and 50 mg/kg. There were no signs of clinical toxicity or evidence of gross lesions in the gastrointestinal tract.

Three cats received two oral 100 mg/kg treatments at 14 day intervals i a study by Dr. Shmidl. Only nausea and vomiting occurred in two animals with no additional clinical signs observed. No significant clinical pathology or histopathology changes occurred.

Dr. S.M. Kruckenberg reports on the oral treatment of seven cats (6 females and 1 male) with a 5 mg/kg dose during all critical periods of reproduction. Two groups of seven cats (6 females and 1 male) each were also treated subcutaneously and intramuscularly with a praziquantel injectable solution with a 5 mg/kg dose during all critical periods of reproduction. Dr. Kruckenberg further evaluated the oral use of praziquantel in one male and three female cats in a controlled study. Two groups of 4 cats (1 male and 3 females) each were also treated subcutaneously and intramuscularly with the praziquantel injectable solution. All treated cats received 3X the label rate. Four females and 1 male served as untreated controls. The treated males received 7 treatments at 2-week intervals throughout the breeding season. Each treated female received a treatment prior to breeding, during the embryogenic period of pregnancy, during late pregnancy and again during lactation. The study confirmed the lack of effects on fertility, conception, fetal development or pregnancy when praziquantel was administered at 3X dosage levels.

Eight cats received three oral doses by Dr. Shmidl at 14-day intervals of either 5X or 10X the labeled rate. No significant clinical signs of toxicity were observed, nor did changes occur for hematology, clinical chemistry and histopathology.

Dr. Shmidl further treated two kittens (4 1/2 to 7 1/2 weeks old) twice at a 14-day interval. The dosage rate was 5X the label dose. Slight depression was observed in one kitten. No significant clinical toxicity signs or clinical pathology and histopathology changes were attributed to this dosage rate.

B. Clinical Field Trial Safety

The tablet formulation was administered to 218 dogs (eight weeks to 16 years of age and 1.5 to 122 lb) in clinical field trials. Seven instances (3.2%) of either vomiting, anorexia, lethargy or diarrhea were reported and were rated as non-significant.

The tablet formulation was further administered to 135 cats (eight weeks to 13 years of age and two to 19 lb) in clinical field trials. One instance of diarrhea and one of salivation (total = 2, 1.5%) were reported and were rated as non-significant.

Five of 61 dogs (8.2%) receiving the positive control drug hydrochloride were observed with side effects of diarrhea and vomiting following the administration of clinically recommended dose.

C. Safety Summary

In summary, the safety index for the use of praziquantel tablets in dogs has been derived using the final tablet formulation (vomition was the pertinent effect with dual treatments of up to 145.8 mg/kg at a 14-day interval). Vomition at high doses is the typical side reaction which prevents serious clinical toxicity signs from occurring. The safety factor is at least 5X the label rate when the product is administered at 14 day intervals to puppies four weeks of age and older.

In summary, the safety index for the use of praziquantel tablets in cats has been derived from controlled studies using the final tablet formulation (vomition was the only effect with dual treatments of 100 mg/kg at a 14-day interval). Vomition at high dosage rates is the typical reaction which prevents significant clinical toxicity signs from occurring. The safety factor is at least 5X the label rate when the product is administered at 14 day intervals to kittens 5 1/2 weeks of age and older.

IV. HUMAN FOOD SAFETY

A. Human Safety Relative to Food Consumption

Data on human safety pertaining to consumption of drug residues in food were not required for approval of this NADA. This product is labeled for use in dogs and cats only, which are non-food animals.

B. Human Safety Relative to Possession, Handling, and Administration

The following warning statement pertaining to the safety of this drug product in humans has been included in the labeling for this product:

WARNING: Keep out of reach of children. Not for human use.

V. AGENCY CONCLUSIONS

Data submitted satisfy the requirements of section 512 of the Act and demonstrate that praziquantel tablets, when used under the proposed conditions of use, are safe and effective for the removal of *Dipylidium caninum* and *Taenia pisiformis* in dogs and removal of *D. caninum* and *Taenia taeniaeformis* from cats.

According to the Center's supplemental approval policy (42 FR64367), this is a Category II change. The supplemental provides for OTC status (as Cutter Tape-Tabs) for the claims mentioned above.

The approval of this supplemental application has no adverse effect on the safety and effectiveness of the new animal drug. Accordingly, this approval did not require a re-evaluation of the safety and effectiveness data in the parent application.

Since *D. caninum* and *Taenia* spp. have many proglottids which may be shed and found in the environment, the general public can adequately diagnose infection with these parasites. The drug has been shown to be safe for use in pregnant and breeding animals. Praziquantel has been on the market for several years and DER summaries do not provide a basis for refusal of approval of OTC status. For these reasons, Cutter Tape-Tabs is given OTC status for the specific indications mentioned above.

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.