

I. GENERAL INFORMATION

A. File Number

NADA 140-893

B. Sponsor

Beecham Laboratories
Div. of Beecham Inc.
501 Fifth Street
Bristol, TN 37620

C. Proprietary Name

CESTEX®

D. Established Name

epsiprantel

E. Dosage and Administration

CESTEX® (epsiprantel) tablets should be administered orally. The recommended dosage of epsiprantel is:

- **Cat** - 1.25 mg/lb of body weight
- **Dog** - 2.5 mg/lb of body weight

Fasting is not necessary or recommended.

Unless exposure to the infected intermediate hosts is controlled, reinfection is likely. In the case of *D. caninum*, an effective flea control program should be instituted.

F. Species/Class

Cats and Dogs

G. Indication

CESTEX® (epsiprantel) tablets are indicated for the removal of the following:

- **Feline cestodes:** *Dipylidium caninum* and *Taenia taeniaeformis*
- **Canine cestodes:** *Dipylidium caninum* and *Taenia pisiformis*

II. EFFECTIVENESS

The effectiveness of CESTEX® in treating feline and canine tapeworms was demonstrated in dose titration, dose confirmation and clinical field studies.

A. Pivotal Studies – Canine

1. Dose Titration Studies

Four dose titration studies were conducted with epsiprantel tablets under the FDA guidelines for cestocides. The dosage levels used were 0, 1.25, 2.5 and 3.75 mg/lb administered orally as a single dose. All dogs were necropsied according to a standard parasitological procedure. Efficacy was calculated as the percent of dogs cleared using the FDA's formula published in the guidelines.

Mean # parasites in control- Mean # parasites in treatment / Mean # parasites in control X 100= % Efficacy

a. Naturally Occurring *Dipylidium caninum*

A study in 40 random source dogs with natural infections of *Dipylidium caninum* was conducted by Dr. Ed Roberson, University of Georgia, Athens, Georgia. The results of this study are displayed in Table #1.

Table 1 Dose Titration - Epsiprantel Naturally Occurring *Dipylidium caninum*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	10	91	0	0	-
1.25	10	5	7	7	94.5
2.5	10	0	10	10	100.0
3.75	10	0	10	10	100.0

Two dogs in the control group and one dog in each of the treatment groups also had concurrent infections with *Taenia pisiformis*. None of the dogs in the treatment groups had *Taenia* present at necropsy, while the control dogs remained positive at necropsy. No adverse effects were noted.

b. Experimentally Induced *Taenia pisiformis*

Dr. Roberson conducted a study in 40 random source dogs utilizing an experimentally induce *Taenia pisiformis* model. The results of this study are displayed in Table #2.

Table 2 Dose Titration - Epsiprantel Experimentally Induced *T. pisiformis*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	10	35	0	0	-
1.25	10	1	9	90	97.1
2.5	10	0	10	100	100.0
3.75	10	0	10	100	100.0

There was no evidence of any adverse reactions in the treated dogs.

c. Naturally Occurring *Dipylidium caninum* and *Taenia pisiformis* Infections

A study in 48 random source dogs with natural infections of *Dipylidium caninum* and *Taenia pisiformis* was conducted by Dr. Thomas J. Kennedy, AEF Research, Inc., Waunakee, Wisconsin. All 48 dogs were positive for *T. pisiformis*. In addition, each group had six dogs with concurrent *D. caninum* infections. The results of this study are shown in Tables #3 and #4.

Table 3 Dose Titration - Epsiprantel Naturally Occurring *T. pisiformis*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	12	404	2	16.7	-
1.25	12	7	7	58.3	98.3
2.5	12	0	12	100	100.0
3.75	12	0	12	100	100.0

Table 4 Dose Titration - Epsiprantel Naturally Occurring *Dipylidium caninum*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	7*	35	1	14.3	-
1.25	0	0	6	100	100.0
2.5	0	0	6	100	100.0
3.75	0	0	6	100	100.0

*One dog was negative pre-treatment but was positive for both *Taenia* and *Dipylidium* and was thus counted as positive pre-treatment.

No side effects were observed in these dogs.

d. Naturally Occurring *Dipylidium caninum* and *Taenia pisiformis* Infections

A study in random source dogs which were naturally infected with *Dipylidium caninum* and/or *Taenia pisiformis* was conducted by Dr. Robert Corwin, University of Missouri, Columbia, Missouri. The results of this study are displayed in Table #5 and #6.

Table 5 Dose Titration - Epsiprantel Naturally Occurring *Dipylidium caninum*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	12*	421	0	0	-
1.25	7	232	6	85.7	5.5
2.5	7	1	6	85.7	99.6
3.75	7	0	7	100	100.0

*3 dogs were negative for *Dipylidium* on pre-treatment but were positive for *Dipylidium* on necropsy and were thus counted as positive pre-treatment.

Table 6 Dose Titration - Epsiprantel Naturally Occurring *Taenia pisiformis*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	7*	56	0	0	-
1.25	8	4	5	62.5	59.3
2.5	10	0	10	100	100
3.75	7	3	6	85.7	94.6

*1 dog was negative for *Taenia* on pre-treatment but was positive for *Taenia* on necropsy and was thus counted as positive pre-treatment.

No adverse reactions occurred in this study. The results from all 4 pivotal dose titration studies support the conclusion that 2.5 mg/lb is the optimum dose of epsiprantel in dogs.

2. Dose Confirmation Studies

Four dose confirmation studies were conducted with epsiprantel tablets according to the FDA guideline for cestocides. The dosage level was 2.5 mg/lb administered orally as a single dose. All dogs were necropsied according to a standard parasitological procedure.

a. Naturally Occurring *Dipylidium caninum*

A study in 20 random source dogs with natural infections of *Dipylidium caninum* was conducted by Dr. Ed Roberson. Epsiprantel tablets were administered as a single oral dose at 2.5 mg/lb. This dosage level was compared to a non-treated control group. The study results are presented in Table #7.

Table 7 Dose Confirmation - Epsiprantel Naturally Occurring *Dipylidium caninum*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	10	327	0	0	-
2.5	10	0	10	100	100

Epsiprantel was effective at a dose of 2.5 mg/lb. No adverse effects were noted in this study.

b. Experimentally Induced *Taenia pisiformis* Infections

A dose confirmation study in 20 random source dogs with experimentally induced *Taenia pisiformis* infections was conducted by Dr. Roberson. Epsiprantel tablets were administered as a single oral dose at 2.5 mg/lb. This dosage level was compared to a non-treated control group. The results of this study are displayed in Table #8.

Table 8 Dose Confirmation - Epsiprantel Experimentally Induced *Taenia pisiformis*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	10	104	0	0	-
2.5	10	0	10	100	100

Epsiprantel was effective in eliminating *Taenia pisiformis* at a dosage level of 2.5 mg/lb. No adverse effects were observed in this study.

c. Naturally Occurring *Dipylidium caninum* and/or *Taenia pisiformis* Infections

A dose confirmation study in 24 random source dogs with natural *Dipylidium caninum* and *Taenia pisiformis* infections was conducted by Dr. Thomas Kennedy. Epsiprantel was administered as a single oral dose at 2.5 mg/lb. This dosage level was compared to a non-treated control group. Fourteen of the 24 dogs had *D. caninum* infections and 20 of 24 had *T. pisiformis* infections. The results of this study are displayed in Tables #9 and #10.

Table 9 Dose Confirmation Epsiprantel Naturally Occurring *Dipylidium caninum*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	8*	110	1	12.5	-
2.5	6	0	6	100	100

*3 dogs were negative pre-treatment but were positive for *Dipylidium caninum* post-treatment and were thus counted as positive pre-treatment.

Table 10 Dose Confirmation - Epsiprantel Naturally Occurring *Taenia pisiformis*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	10*	294	1	10	-
2.5	10	0	10	100	100

*One dog was negative pre-treatment but was positive for *Taenia pisiformis* on post-treatment and was thus counted as positive pre-treatment.

In this study, 2.5 mg/lb of epsiprantel eliminated 100% of the *D. caninum* and *T. pisiformis* infections. No adverse reactions were noted in this study.

d. Naturally Occurring *Dipylidium caninum* and/or *Taenia pisiformis* Infections

A dose confirmation study in 36 random source dogs with natural *Dipylidium caninum* and/or *Taenia pisiformis* infections was conducted by Dr. Robert Corwin. Epsiprantel was administered as a single oral dose at

2.5 mg/lb. This dosage level was compared to a non-treated control group. The results of this study are shown in Table #11 and #12.

Table 11 Dose confirmation - Epsiprantel Naturally Occurring *Dipylidium caninum*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	10**	909	0	0	-
2.5	10*	0	10	100	100

*3 dogs were positive for both *Taenia* and *Dipylidium*.

**4 dogs were positive for *Taenia* on pre-treatment but on necropsy were found to have *Dipylidium* and thus were counted as positive for *Dipylidium* on pre-treatment.

Table 12 Dose Confirmation - Epsiprantel Naturally occurring *Taenia pisiformis*

Treatment Group (mg/lb)	No. Dogs	No. Parasites	No. Dogs Cleared	% Dogs Cleared	% Efficacy
0	12*	237	1	8.3	-
2.5	14	0	14	100	100

*1 dog was positive only for *Dipylidium* on pre-treatment but was found to be infected with both *Taenia* and *Dipylidium* on necropsy and thus were counted positive on pre-treatment.

Again, 2.5 mg/lb of epsiprantel eliminated 100% of the *D. caninum* and *T. pisiformis* infections. No adverse reactions were noted in this study.

3. Clinical Field Study

A clinical field study was initiated to determine the efficacy of epsiprantel against canine tapeworms. The study was conducted as a blind, parallel group, multi center trial wherein the test drug, epsiprantel, was compared to the active control, praziquantel.

Dogs of any age, breed and either sex with confirmed tapeworm infections were included in this study. The diagnosis was based on identification of tapeworm segments or eggs on fecal flotation.

The dosage of epsiprantel was 2.5 mg/lb. The dosage of DRONCIT (praziquantel) was that recommended in the package insert. The drugs were administered as a single treatment.

Post treatment examination was conducted 7 to 30 days following treatment. In order for the tapeworms to be considered eliminated, both the clinical observation and the fecal flotation must be negative.

A total of 17 investigators in 11 states participated in this study and are listed below:

- Dr. John Paul Arnold, Tyler, Texas 75701
- Dr. Waybern D. Yates, Raytown, MO 64133
- Drs. Dean Small and James Humphrey, Overland Park, KS 66204
- Dr. Robert Cannon, Kansas City, MO 64111
- Drs. Alan Shriro & Richard Benjamin, Berkeley, CA 94704
- Dr. Steven Krome, Walnut Creek, CA 94596
- Dr. James Fish, Jacksonville, FL 32210
- Drs. Paul & Janis Cleland, Lilburn, GA 30247
- Dr. Scott Richter, Marietta, GA 30062
- Drs. Richard Roberts & Vernon Thornton, Hanover, MA 02339
- Dr. Mark Van Ness, Houston, TX 77027
- Dr. Lynn Buzhardt, Zachary, LA 70791
- Dr. Ken Acre, Winter Park FL 32789
- Dr. Robert Klostermann, Middleton, WI 53562
- Dr. Randall Herman, New Hope, MN 55427
- Dr. Danielle Garrison, Taylorsville, MS 39168
- Dr. Ken Lambrecht, Madison, WI 53711

A total of 252 evaluable cases was enrolled. A total of 255 tapeworms was identified during the pre-treatment examination in these 252 cases. Epsiprantel eliminated 106/108 (98%) of the *D. caninum* versus 120/120 (100%) for DRONCIT (praziquantel). Both drugs eliminated 100% of the *Taenia pisiformis*. Concurrent therapy included antibiotics, diethylcarbamazine citrate, ivermectin, insecticides, anti inflammatory, and nematocide. No drug incompatibilities were noted.

B. Pivotal Studies Feline

1. Dose Titration Studies

Three dose titration studies were conducted with epsiprantel tablets under the FDA guidelines for cestocides. The dosage levels used were 0, 0.625, 1.25 and 2.75 mg/lb administered orally as a single dose. All cats were necropsied according to a standard parasitological procedure. Efficacy was calculated as the percent of cats cleared using the FDA's formula published in the guidelines.

Mean # parasites in control

Mean # parasites in treated / Mean # parasites in control X 100 = % Efficacy

Two studies were conducted to evaluate the efficacy of epsiprantel against *Dipylidium caninum* in the cat. These studies were conducted by Dr. Tom Yazwinski, University of Arkansas, Fayetteville, AR, and Dr. Alan Kocan, Oklahoma State University, Stillwater, OK. A total of 54 parasitic infections were treated. The *Dipylidium* results of these studies are presented in Table #13.

Table 13 *Dipylidium caninum* Dose Titration Studies

Dosage (mg/lb)	Dr. Tom Yazwinski University of Arkansas Fayettevill, AR				Dr. Alan Kocan Oklahoma State University Stillwater, OK			
	0	0.625	1.25	2.5	0	0.625	1.25	2.5
No. Cats	8	8	7	9	4	7	5	6
No. Parasites	596	14	0	1	25	3	4	0
No. Cats Cleared	0	5	7	8	0	6	4	6
% Efficacy	-	97.7	100	99.9	-	93.2	87.2	100

Two studies were conducted to evaluate epsiprantel against *Taenia taeniaeformis*. These studies were conducted by the following two investigators: Dr. Tom Kennedy, AEF Research, Waunauke, WI and Dr. Al Kocan, Oklahoma State University, Stillwater, OK. A total of 62 *Taenia* infected cats were treated and then necropsied. The results of these studies are presented in Table #14.

Table 14 *Taenia taeniaeformis* Dose Titration Studies

Dosage (mg/lb)	Dr. Tom Kennedy AEF Research Waunakee, WI				Dr. Alan Kocan Oklahoma State University Stillwater, OK			
	0	0.625	1.25	2.5	0	0.625	1.25	2.5
No. Cats	8	8	8	8	9	8	7	6
No. Parasites	73	15	1	0	35	0	0	0
No. Cats Cleared	0	2	7	8	0	8	7	6
% Efficacy	-	79.5	98.6	100	-	100	100	100

2. Dose Confirmation Studies

Following the completion of the dose titration studies, a series of dose confirmation studies were undertaken. Epsiprantel was supplied as film coated tablets as in the dose titration studies. Four tablet concentrations were available: 6.25, 12.5, 25, and 50 mg of epsiprantel activity per tablet.

Two studies were conducted according to the Agency's guidelines. The dosage level used in these studies was the previously selected optimum dose of 1.25 mg/pound administered orally one time. This dosage level was compared to a non-treatment group. All cats were necropsied following treatment utilizing a standard parasitological procedure by removal of the entire gastrointestinal tract from the stomach to the rectum. The digestive tract was open and contents washed over a sieve. The mucosa was also observed for attached worms. Efficacy was calculated as percent of cats cleared and using the Agency's formula published in the guidelines.

Mean # parasites in control

Mean # parasites in treated / Mean # parasites in control X 100 = % Efficacy

All dose confirmation studies were done in cats with natural infections. The following two investigators participated in these studies: Dr. Tom Yazwinski, University of Arkansas, Fayetteville, AR and Dr. Alan Kocan, Oklahoma State University, Stillwater, OK. Table #15 shows the results of the dose confirmation studies in cats infected with *Dipylidium caninum* and *T. taeniaeformis*.

Table 15 Dose Confirmation Studies

	<i>Dipylidium caninum</i>				<i>Taenia taeniaeformis</i>	
	Dr. Tom Yazwinski U. of AR		Dr. Alan Kocan OK State Univ.		Dr. Alan Kocan OK State Univ.	
Dosage (mg/lb)	0	1.25	0	1.25	0	1.25
No. Cats	10	10	5	6	8	6
No. Parasites	210	0	43	0	72	0
No. Cats Cleared	0	10	0	6	-	-
% Efficacy	-	100	-	100	-	100

During the course of these studies, 14 *T. taeniaeformis* infected cats were entered into this study. Six (6) *Taenia* cats were treated with 1.25 mg/lb of epsiprantel. Eight (8) cats served as non-treated controls. The results of these studies are presented in Table #15.

3. Clinical Field Study

A clinical field study was initiated to determine the efficacy of epsiprantel against feline tapeworms. The study was conducted as a blind, parallel group, multi-center trial wherein the test drug, epsiprantel, was compared to the active control, praziquantel.

Cats of any age, breed and either sex with confirmed tapeworm infections were included in this study. The diagnosis was based on identification of tapeworm segments or eggs on fecal flotation.

The dosage of epsiprantel was 1.25 mg/lb. The dosage of DRONCIT (praziquantel) was that recommended in the package insert. The drugs were administered as a single treatment.

Post-treatment examination was conducted 7 to 30 days following treatment. In order for the tapeworms to be considered eliminated, both the clinical observation and the fecal flotation must be negative.

A total of 17 investigators in 9 states participated in this study and are listed below:

- Dr. Ken Acre, Winter Park, FL 32789
- Dr. John Paul Arnold, Tyler, Texas 75701
- Dr. Lynn Buzhardt, Zachary, LA 70791
- Drs. Richard M. Coe, Jr. and Susan Coe, Charlotte, NC 28205
- Dr. Thomas H. Elston, Boston, MASS 02215
- Dr. James W. Eubanks, Winston Salem, NC 27104
- Dr. James Fish, Jacksonville, FL 32210
- Dr. R. E. Killough, Charlotte, NC 28211
- Dr. Steven Krome, Walnut Creek, CA 94596
- Dr. Robert Neunzig, Gastonia, NC 28052
- Dr. Scott Richter, Marietta, GA 30062
- Dr. Don S. Robertson, Winston Salem, NC 27106
- Dr. Arthur C. Seale, Shreveport, LA 71105
- Dr. David K. Selleck, Fayetteville, GA 30214
- Dr. David Thompson, Asheville, NC 28804
- Dr. Mark Van Ness, Houston, TX 77027
- Dr. Waybern D. Yates, Raytown, MO 64133

A total of 225 evaluable cases was enrolled. A total of 226 tapeworms was identified during the pre-treatment examination in these 225 cases. Epsiprantel eliminated 100% (83/83) of the *D. caninum* as did DRONCIT (praziquantel) (102/102). Both drugs eliminated 100% of the *Taenia* identified.

Concurrent therapy included antibiotics, vaccines, insecticides, and tranquilizers/anesthetics. No drug incompatibilities were noted.

C. Corroborative Studies – Feline

1. Dose Titration Studies

Two dose titration studies were conducted with epsiprantel tablets under the FDA guidelines for cestocides. The dosage levels used were 0, 0.625, 1.25 and 2.75 mg/lb administered orally as a single dose. All cats were necropsied according to a standard parasitological procedure. Efficacy was calculated as the percent of cats cleared using the FDA's formula published in the guidelines.

Mean # parasites in control - Mean # parasites in treated / Mean # parasites in control X 100 = % Efficacy

Two studies were conducted to evaluate epsiprantel against *Taenia taeniaeformis*. These studies were conducted by the following investigators: Dr. Tom Yazwinski, University of Arkansas, Fayetteville AR and Dr. Dan Moncol, North Carolina State University, Raleigh, NC. A total of 20 *Taenia* infected cats were treated and then necropsied. These results of these studies are presented in Table #16.

Table 16 Dose Titration Studies *Taenia taeniaeformis*

	Dr. Tom Yazwinski University of Arkansas Fayetteville, AR				Dr. Dan Moncol N. Carolina State University Raleigh, NC			
Dosage (mg/lb)	0	.625	1.25	2.5	0	.625	1.25	2.5
No. Cats	5	1	4	2	2	2	2	2
No. Parasites	30	0	0	0	24	0	0	0
No. Cats Cleared	0	1	4	2	0	2	2	2
% Efficacy	-	100	100	100	-	100	100	100

2. Dose Confirmation Studies

Following the completion of the dose titration studies, a series of dose confirmation studies were undertaken, Epsiprantel was supplied as film coated tablets as in the dose titration studies. Four tablet concentrations were available: 6.25, 12.5, 25, and 50 mg of epsiprantel activity per tablet.

Three studies were conducted according to the Agency's guidelines. The dosage level used in these studies was the previously selected optimum dose of 1.25 mg/pound administered orally one time. This dosage level was compared to a non-treatment group. All cats were necropsied following treatment utilizing a standard parasitological procedure by removal of the entire gastrointestinal tract from the stomach to the rectum. The digestive tract was open and contents washed over a sieve. The mucosa was also observed for attached worms. Efficacy was calculated as percent of cats cleared and using the Agency's formula published in the guidelines.

Mean # parasites in control

Mean # parasites in treated / Mean # parasites in control X 100 = Efficacy

All three dose confirmation studies were done in cats with natural infections. The following three investigators participated in these studies: Dr. Tom Yazwinski, University of Arkansas, Fayetteville, AR; Drs. Smith and Malone, Louisiana State University, Baton Rouge, LA; and Dr. Tom Kennedy, AEF Research, Waunakee, WI. Table #17 shows the results of the dose confirmation studies in cats infected with *Dipylidium caninum*.

Table 17 Dose Confirmation Studies *Dipylidium Caninum*

	Drs. Smith & Malone LA State U.		Drs. T. Kennedy & Poster AEF Research	
Dosage (mg/lb)	0	1.25	0	1.25
No. Cats	3	4	3	2
No. Parasites	64	0	106	1
No. Cats Cleared	0	4	0	1
% Efficacy	-	100	-	98.6

During the course of these studies, 17 *T. taeniaeformis* infected cats were entered into this study. Seven (7) *Taenia* cats were treated with 1.25 mg/lb of epsiprantel. Ten (10) cats served as non-treated controls. The results of these studies are presented in Table #18.

Table 18 *Taenia taeniaeformis* Dose Confirmation Studies

	Dr. Tom Yazwinski* Univ. of AR		Drs. Smith & Malone LA State U.		Drs. T. Kennedy & Poster AEF Research	
Dosage (mg/lb)	0	1.25	0	1.25	0	1.25
No. Cats	5	1	4	4	1	2
No. Parasites	32	0	10	0	4	0
No. Cats Cleared	0	1	1	4	0	2
% Efficacy	-	100	-	100	-	100

*Three cats were negative pre-treatment but were positive with *T. taeniaeformis* on post-treatment. Thus, these were counted as positive pre-treatment.

3. European Non Terminal Dose Titration Studies: Beecham Pharmaceuticals, Walton Oaks, England

A non-terminal study was conducted in England under the direction of Dr. Ian Hood in 55 cats with natural *Dipylidium caninum* infections and experimentally induced with *Taenia taeniaeformis*. Epsiprantel was administered as a powder in gelatin capsules at dosages ranging from 0.23 to 13.64 mg/lb. The drug was considered to have cestocidal activity if the animal stopped passing gravid segments in their feces (9-10 days post-treatment). It is recognized that non-terminal studies are useful but cannot be relied upon for proof of complete efficacy. Bearing this in mind, the following results were obtained:

Table 19 Dose Titration Studies - Screening Clinical Efficacy - Non Terminal Studies Natural & Experimentally Induced

Dose mg/lb	<i>Dipylidium caninum</i>			<i>Taenia taeniaeformis</i>		
	# Cats Infected	# Cats Cleared	% Cats Cleared	# Cats Infected	# Cats Cleared	% Cats Cleared
0.23	10	5	50	10	5	50
0.45	20	16	80	20	19	95
1.14	20	16	80	20	19	95
2.24	1	1	100	1	1	100
4.55	-	-	-	1	1	100
4.55	-	-	-	2	2	100

4. European Terminal Dose titration Screening Studies:

A dose titration study was conducted by administering a single oral dose of epsiprantel capsule to 20 naturally infected *D. caninum* cats which were experimentally infected with *T. taeniaeformis*. Cats were randomly allocated to treatment groups. The dose of epsiprantel was calculated and placed in a capsule. Cats had a routine parasitic necropsy examination three to four days after treatment. This necropsy date is shorter than the USA guideline calls for but the mucosa was scrapped off and together with washing from the intestinal tract was washed through a 600 um sieve. The retained debris was then examined under a dissecting microscope at X10 magnification. The *Dipylidium* results are present in Table #20 and the *Taenia* results in Table #21.

Table #20 shows that all three dose levels of epsiprantel eliminated all the *Dipylidium* in these cats.

Table 20 Controlled Tests with Epsiprantel against *Dipylidium Caninum* in Cats Walton Oaks, England

Treatment	Dose mg/lb	No. Cats Pos	No. Cats Neg	Total No. <i>D. caninum</i> Retained	% Efficacy
Control	0	4	0	29	-
Epsiprantel	1.14	4	4	0	100
Epsiprantel	2.27	4	4	0	100
Epsiprantel	3.41	4	4	0	100
Epsiprantel	2.27	4	4	0	100

Table #21 presents the results for the *Taenia taeniaeformis* in this study. One cat in the 1.14 mg/lb. and 3.41 mg/lb. groups each had one *Taenia* worm at necropsy. The control had 28 parasites.

Table 21 Controlled Tests with Epsiprantel against *Taenia Taeniaeformis* Cats Walton Oaks, England

Treatment	Dose mg/lb	No. Cats Pos	No. Cats Neg	Total No. <i>T. taeniaeformis</i> Retained	% Efficacy
Control	0	4	0	28	-
Epsiprantel	1.14	4	3	1	96.4
Epsiprantel	2.27	4	4	0	100
Epsiprantel	3.41	4	4	0	196.4
Epsiprantel	2.27	4	4	0	100

*Number Tapes in Controls minus number in treated group divided by Number Tapes in Controls X 100

No adverse reactions were noted during this study. Epsiprantel had no apparent effect on *T. cati*.

III. TARGET ANIMAL SAFETY

A. Pivotal Studies - Canine

1. Target Species Toxicity Study

The objective of this study was to observe any toxic effects of epsiprantel tablets when administered orally to young dogs. This study was conducted by Dr. Abbott S. D'Ver, White Eagle Laboratories, Doylestown, Pennsylvania.

Twelve male and twelve female 5-6 month old beagles were used. Prior to treatment, the dogs were randomized into four groups, each consisting of three males and three females.

This study was an open evaluation of epsiprantel tablets utilizing three dosage levels and a control group. The drug was administered orally for three days at a dose rate of 2.5, 7.5 and 12.5 mg/lb. The following were evaluated: general clinical parameters. hematology, blood chemistry, gross and microscopic lesion. Twenty-four hours after the third dose, one-half of the dogs were necropsied. The remainder was necropsied 48 hours after the last dose.

No abnormal values considered related to the test drug were obtained in regard to body temperature, heart rate, respiratory rate, body weight, food consumption and general appearance.

Hematology and blood chemistries did not reveal any drug related differences between the test and control dogs. No gross or microscopic lesions related to epsiprantel were detected.

2. Repeat Dose Toxicity in Dogs

A 14 day repeat dose study in dogs was conducted by Dr. Cockburn, Beecham Pharmaceuticals Research Division, Essex, England. Epsiprantel was administered orally to dogs at dose levels of 10, 100, and 500 mg/kg/day for 14 days. Physical symptoms were limited to isolated occurrence of emesis at all dose levels. Food intake was unaffected by treatment but body weight gain was increased in females at all dose levels. Hematology and blood chemistry

changes consisted of increased alkaline phosphatase activity and reduced total white blood cell counts at the high dose level. Reduced lymphocyte counts in females only were noted in the 100 and 500 mg/kg/day group. A low incidence of slight proteinuria was detected at the intermediate and high dose levels. Organ weight variations consisted of increased liver weights in two of the four high dose dogs, increased pituitary weight in one of the two females at the intermediate and high dose levels. Histopathology revealed no significant findings.

B. Corroborative Studies Canine

1. Canine Tolerance Studies

Single dose oral tolerance studies with epsiprantel were conducted by Dr. B.R. Manger, Beecham Pharmaceuticals Research Division, ENGLAND.

A single oral dose of 100 mg/kg produced no overt toxicity in 7 to 10 week old beagle puppies, nor in an adult collie. Similarly, no toxic side effects were detected in adult dogs given a single oral dose of 200 mg/kg. No drug related changes in SGPT, SGOT and BUN were noted in blood samples from dogs dosed at 200 mg/kg.

2. Repeat Dose Toxicity in Puppies

A three day repeat dose toxicity study in dogs was conducted by Dr. Abbott D'Ver. Epsiprantel was administered orally to seven week old puppies for three consecutive days at a dose of 7.5 mg/lb. No clinical symptoms or effects on body weight were noted during the study. No drug related differences between the test and control dogs were detected in the hematology and blood chemistries. No gross or histopathologic lesions related to the drug were detected.

3. Greyhound Safety Study

Epsiprantel tablets were administered orally to greyhounds for three consecutive days at a dosage of 7.5 mg/lb. This study was conducted by Dr. Ken Acre, Winter Park, Florida.

Clinical evaluation revealed no adverse effect on feed consumption, temperature, heart rate, respiratory rate, general appearance, fecal consistency and body weight.

Hematology and blood chemistries revealed no drug related effects.

C. Pivotal Studies – Feline

1. Target Species Toxicity Study

The objective of this study was to observe any toxic effects of epsiprantel tablets when administered orally to young cats. This study was conducted by Dr. Abbott S. D'Ver, White Eagle Laboratories, Doylestown, Pennsylvania.

Twelve male and twelve female 4-5 month old cats were used. Prior to treatment, the cats were randomized into four groups, each consisting of three males and three females.

This study was an open evaluation of epsiprantel tablets utilizing three dosage levels and a control group. The drug was administered orally for three days at a dose rate of 1.25, 3.75 and 6.25 mg/lb. The following parameters evaluated: general clinical parameters, hematology, blood chemistry, gross and microscopic lesions. Twenty-four hours after the third dose, one half of the cats were necropsied. The remainder was necropsied 48 hours after the last dose.

No abnormal values considered related to the test drug were obtained in regard to general clinical parameters, hematology and blood chemistries. No gross or microscopic lesions related to epsiprantel were detected.

2. Feline Tolerance Studies

Single and repeat oral tolerance studies with epsiprantel were conducted by Dr. David Wishart, Beecham Pharmaceuticals Research Division, ENGLAND.

A single oral dose of 0.5 to 30 mg/kg produced no overt toxicity. At a single dose of 50 mg/kg one of five kittens vomited two hours after treatment and displayed trembling for two hours. At 100 mg/kg, two out of 13 animals vomited within a day of treatment.

In the repeat dose study, six cats received epsiprantel at 50 or 100 mg/kg daily for four consecutive days. No ill effects were noted in these cats.

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:

A warning statement pertaining to the safety of this drug product in humans has been included in the labeling for this product. The statement is

WARNING: For use in dogs (and cats, on the 12.5 mg label) only. Keep out of reach of children. Not for use in humans.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrated that epsiprantel tablets, when used under the labeled conditions of use, is safe and effective for the removal of *Dipylidium caninum* and *Taenia pisiformis* from dogs and the removal of *Dipylidium caninum* and *Taenia taeniaeformis* from cats.

Because safety of this drug has not been established for use in pregnant or breeding animal, it is not safe for use except under the supervision of a licensed veterinarian. Therefore, epsiprantel is approved as a veterinary prescription drug.

VI. LABELING

1. Cestex® Package Insert
2. Cestex® Package Insert
3. Cestex® Package label 12.5 mg
4. Cestex® Package label 25 mg
5. Cestex® Package label 50 mg
6. Cestex® Package label 100 mg

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.