Date of Approval: June 29, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-275

PROFENDER Topical Solution

emodepside / praziquantel

Cats

PROFENDER Topical Solution is indicated for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats.

Sponsored by:

Bayer HealthCare LLC

Animal Health Division

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I. GENERAL INFORMATION:

A. File Number: NADA 141-275

B. Sponsor: Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

Drug Labeler Code: 000859

C. Proprietary Name(s): PROFENDER Topical Solution

D. Established Name(s): emodepside / praziquantel

E. Pharmacological Category: antiparasitic

F. Dosage Form(s): solution

G. Amount of Active Ingredient(s): Each mL contains 21.4 mg emodepside and 85.7 mg praziquantel

H. How Supplied: Unit applicator tube

40 - 0.35 mL tubes (10 blisters of 4 tubes)
40 - 0.70 mL tubes (10 blisters of 4 tubes)
24 - 1.12 mL tubes (6 blisters of 4 tubes)

I. How Dispensed: Rx

J. Dosage(s):

Recommended minimum dosage is 1.36 mg/lb (3 mg/kg) emodepside and 5.45 mg/lb (12 mg/kg) praziquantel. Administer the entire contents of a unit applicator tube of PROFENDER Topical Solution topically one time as specified in the following table:

Cat Weight	PROFENDER Topical Solution	Volume (mL)	mg Emodepside	mg Praziquantel
2.2 - 5.5 lbs	Small	0.35	7.5	30.0
> 5.5 - 11.0 lbs	Medium	0.70	15.0	60.1
> 11.0 – 17.6 lbs	Large	1.12	24.0	96.1

*Cats over 17.6 lbs should be treated with the appropriate combination of tubes.

K. Route(s) of Administration: Topical

L. Species/Class(es): Cats

M. Indication(s): PROFENDER Topical Solution is indicated for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats.

II. EFFECTIVENESS:

A. Dosage Characterization:

Studies using pilot formulations of emodepside and praziquantel were conducted to determine the appropriate dose of emodepside or praziquantel against nematode or cestode infections, respectively. All the pilot studies used both active ingredients in various combinations.

The effectiveness of 1, 2, and 4 mg of emodepside per kg body weight was tested against *Toxocara cati* and/or *Ancylostoma* species (spp.). Two studies showed that 1 mg/kg emodepside was > 90% effective against *Ancylostoma* spp. but a third showed that dose only 51% effective against *Ancylostoma braziliense.* Another study showed that 1 mg/kg was 94.6% effective against *Ancylostoma* spp. but only 42% effective against *T. cati.* These studies showed that the appropriate dose of emodepside against *T. cati* was between 1 and 2 mg/kg but with variable consistency. A dose of 3 mg/kg was chosen to ensure consistency. This was confirmed in study number 151.077, "Evaluation of the Efficacy of Different Dose Levels of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Mature *Toxocara cati* Infection in Cats." Cats were dosed with 1.5, 3, and 6 mg emodepside per kg body weight. All three doses were 100% effective against *T. cati* (see page 4).

The effectiveness of 4, 8, and 12 mg of praziquantel per kg body weight was tested against *Dipylidium caninum.* In the first study, only 12 mg/kg was 100% effective. A second study evaluated doses of 8, 10, and 12 mg/kg with 10 and 12 mg/kg showing 100% effectiveness. A final pilot study using 6, 12, and 24 mg/kg praziquantel showed 95%, 90% and 100% effectiveness, respectively. The middle dose of 12 mg praziquantel per kg body weight was chosen. This dose was confirmed in study

number 151.601, "Evaluation of the Efficacy of Different Dose Levels of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Dipylidium caninum* Infection in Cats." Naturally infected cats were dosed with 6, 12, and 24 mg praziquantel per kg body weight. The low dose was 84% effective while the two higher doses were both 100% effective against *D. caninum* (see page 17).

B. Substantial Evidence:

Statistical Methods

Each laboratory effectiveness study used the same analysis for effectiveness. Log worm counts for the treatment groups were compared to log worm counts for the control groups by means of an analysis of variance contrast. All statistical tests were two-tailed and conducted at an α of 0.05. Drug effectiveness was calculated as:

% Effectiveness = (N2 – N1)/N2 x 100
N1 = Geometric mean worm count for treatment group
N2 = Geometric mean worm count for control group

Nematode Studies (*Toxocara cati*)

1) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Toxocara cati* Infection in Cats. (Study # 151.619, Report # 75618)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against mature natural *T. cati* infections in the cat after one topical application.

Study Investigator: Dr. David Young

Location: Young Veterinary Research Services, Turlock, CA

Animals: 20 cats (13 domestic shorthair, 5 domestic longhair and 2 Siamese), (8 males and 12 females), approximately 0.7 to 3 years of age, weighing from 2.5 to 6.18 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats naturally infected with *T. cati* were randomly assigned to two treatment groups. Following a 10-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving adult *T. cati* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with natural *T. cati* in cats is shown in the following table:

Table 1: Effectiveness of Emodepside/Praziquantel against adult *T. cati*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	10.6	n/a*
Group 2: emodepside/praziquantel	0	100

*Not applicable

Adverse Reactions: There were incidences of constricted or dilated pupils, loose stool, and diarrhea in both treatment groups throughout the study.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against natural adult *T. cati* infections in cats.

2) Evaluation of the Efficacy of Different Dose Levels of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Mature *Toxocara cati* Infection in Cats. (Study # 151.077, Report # 75607)

Purpose: The study was conducted to determine the safety and effectiveness of three dose levels of emodepside and praziquantel against mature induced *T. cati* infections in the cat after one topical application.

Study Investigator: Dr. John W. McCall

Location: TRS Labs Inc., Athens, GA

Animals: 32 domestic shorthair cats (16 males and 16 females), approximately 6 to 7 months old, weighing from 2.1 to 4.4 kg, 8 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 1.5 mg/kg emodepside and 6 mg/kg praziquantel
Group 3: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 4: 6 mg/kg emodepside and 24 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats experimentally infected with *T. cati* were randomly allocated to four groups. Following a 10-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving adult *T. cati* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with adult *T. cati* in cats is shown in the following table:

Table 2: Effectiveness of Emodepside/Praziquantel against adult *T. cati*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	26.5	n/a
Group 2: 1.5 mg/kg emodepside/6 mg/kg praziquantel	0	100
Group 3: 3 mg/kg emodepside/12 mg/kg praziquantel	0	100
Group 4: 6 mg/kg emodepside/24 mg/kg praziquantel	0	100

Adverse Reactions: None reported.

Conclusions: All three doses of emodepside/praziquantel topical solution were 100% effective against induced adult *T. cati* infections in cats.

3) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Immature (Fourth Stage Larvae and Immature Adults) *Toxocara cati* in Cats. (Study # 151.078, Report # 75610)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against immature *T. cati* infections in the cat after one topical application.

Study Investigator: Dr. Craig Reinemeyer

Location: East Tennessee Clinical Research, Knoxville, TN

Animals: 32 domestic shorthair kittens (16 males and 16 females), approximately 12 to 13 weeks of age, weighing from 1.3 to 1.9 kg, 8 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 3: placebo (vehicle without active ingredients)
Group 4: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 15 days

Study Design: Cats experimentally infected with *T. cati* were randomly allocated to four groups. Groups 1 and 2 were treated on day 14 and groups 3 and 4 were treated on day 24 to target different immature stages. Following a 5-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *T. cati* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with fourth stage larvae *T. cati* in cats is shown in the following table:

Table 3: Effectiveness of Emodepside/Praziquantel against fourth stage larvae *T. cati*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	15.0	n/a
Group 2: emodepside/praziquantel	0.1	99.4
Group 3: placebo	12.0	n/a
Group 4: emodepside/praziquantel	0	100

Effectiveness of emodepside/praziquantel topical solution against immature adult *T. cati* in cats is shown in the following table:

Table 4: Effectiveness of Emodepside/Praziquantel against immature adult *T. cati*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 3: placebo	28.2	n/a
Group 4: emodepside/praziquantel	0	100

Adverse Reactions: Salivation, gagging, lethargy, and a swollen tongue were seen in one cat treated with the vehicle placebo.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 99.4% and 100% effective against infections with fourth stage larvae *T. cati* and 100% effective against infections with immature adult *T. cati* in cats.

4) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Immature (Fourth Stage Larvae and Immature Adults) of *Toxocara cati* in Cats. (Study # 143.084, Report # 27363)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against immature *T. cati* infections in the cat after one topical application.

Study Investigator: Dr. Christian Epe

Location: School of Veterinary Medicine, Hanover, Germany

Animals: 32 European shorthair kittens (16 males and 16 females), approximately 10 to 13 weeks old, weighing from 0.8 to 1.5 kg, 8 per group

Treatment Groups:[1] Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 3: placebo (vehicle without active ingredients)
Group 4: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 33 days

Study Design: Cats experimentally infected with *T. cati* were randomly allocated to four groups. Cats in groups 1 and 2 were treated on study day 5 and groups 3 and 4 were

[1] Groups 1 and 2 were included in the study but did not generate data toward approval of emodepside/praziquantel topical solution for cats.

treated on study day 28 to target different immature stages. All cats were euthanized and necropsied on day 33.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *T. cati* were recovered, counted, and identified.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with fourth stage larvae *T. cati* in cats is shown in the following table:

Table 5: Effectiveness of Emodepside/Praziquantel against fourth stage larvae *T. cati.*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 3: placebo	8.25	n/a
Group 4: emodepside/praziquantel	0	100

Adverse Reactions: None reported.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against induced infection with fourth stage larvae *T. cati* in cats.

5) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Mature *Toxocara cati* in Cats. (Study # 141.000, Report # 27355)

Purpose: The study was conducted to demonstrate non-interference of praziquantel when combined with emodepside against induced mature *T. cati* infection in the cat.

Study Investigator: Dr. Christian Epe

Location: School of Veterinary Medicine, Hanover, Germany

Animals: 31 European shorthair kittens (14 males and 17 females), 12 to 14 weeks old, weighing 0.9 to 1.6 kg, 7 to 8 per group

Treatment Groups: Group 1: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 2: 3 mg/kg emodepside
Group 3: 12 mg/kg praziquantel
Group 4: placebo (vehicle without active ingredients)

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 14 days

Study Design: Cats experimentally infected with *T. cati* were randomly allocated to four groups about a week before treatment. Following a 7-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *T. cati* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infection with adult *T. cati* in cats is shown in the following table:

Table 6: Effectiveness of Emodepside/Praziquantel against adult *T. cati*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: emodepside/praziquantel	0.0	100
Group 2: emodepside alone	0.0	100
Group 3: praziquantel alone	9.8	n/a
Group 4: placebo	3.6	n/a

Adverse Reactions: None reported.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against *T. cati*. The emodepside alone was 100% effective. The addition of praziquantel did not interfere with the effectiveness of emodepside against *T. cati.* The praziquantel showed no activity against *T. cati.*

Nematode Studies (*Ancylostoma tubaeforme*)

1) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Ancylostoma tubaeforme* Infection in Cats. (Study # 151.075, Report # 75609)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against natural adult *A. tubaeforme* infections in the cat after one topical application.

Study Investigator: Dr. David Young

Location: Young Veterinary Research Services, Turlock, CA

Animals: 20 cats (domestic shorthair, domestic longhair and Siamese), 2 males and 18 females, approximately 6 months to 3 years old, weighing 2.1 to 4.5 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats naturally infected with *A. tubaeforme* were randomly allocated to two groups. Following a 10-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving adult *A. tubaeforme* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with adult *A. tubaeforme* in cats is shown in the following table:

Table 7: Effectiveness of Emodepside/Praziquantel against adult *A. tubaeforme*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	16.8	100
Group 2: emodepside/praziquantel	0	n/a

Adverse Reactions: None reported.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against natural adult *A. tubaeforme* infections in cats.

2) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Ancylostoma tubaeforme* Infection in Cats. (Study #151.503, Report # 75613)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against natural adult *A. tubaeforme* infections in the cat after one topical application.

Study Investigator: Tony Janes

Location: Central Arizona Veterinary Laboratory (CAVL), Amarillo, TX

Animals: 20 domestic shorthair and longhair cats (11 males and 9 females), approximately 10 months to 3 years old, weighing from 2.5 to 6.2 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats naturally infected with *A. tubaeforme* were randomly assigned to two treatment groups. Following a 10-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *A. tubaeforme* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against natural infections with *A. tubaeforme* in cats is shown in the following table:

Table 8: Effectiveness of Emodepside/Praziquantel against adult *A. tubaeforme*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	4.1	n/a
Group 2: emodepside/praziquantel	0	100

Adverse Reactions: Some cats in each group experienced diarrhea and loose stool with a higher incidence after dosing. Two cats in the treated group had respiratory congestion which started 5 days after treatment and resolved before study end.

Conclusions: A single topical dose of emodepside and praziquantel was 100% effective against natural infections with adult *A. tubaeforme* infection in cats.

3) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Immature [Fourth Stage (L4) and Immature Adults] *Ancylostoma tubaeforme* in Cats. (Study # 141.011, Report # 27347)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against induced immature *A. tubaeforme* infections in the cat

after one topical application

Study Investigator: Dr. F. H. M. Borgsteede

Location: ID-Lelystad, Institute for Animal Health, Lelystad, Netherlands

Animals: 32 domestic shorthair kittens (17 males and 15 females), approximately 11 to 16 weeks old, weighing 0.7 to 2.2 kg, 8 per group

Treatment Groups:
Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 3: placebo (vehicle without active ingredients)
Group 4: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 19 days

Study Design: Cats experimentally infected with *A. tubaeforme* were randomly allocated to four groups. Groups 1 and 2 were treated on day 7 and groups 3 and 4 were treated on day 14 to target different immature stages. Following a 5-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving immature *A. tubaeforme* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with fourth stage larvae of *A. tubaeforme* in cats is shown in the following table:

Table 9: Effectiveness of Emodepside/Praziquantel against fourth stage larvae *A. tubaeforme*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	137.8	n/a
Group 2: emodepside/praziquantel	1.8	98.7
Group 3: placebo	29.4	n/a
Group 4: emodepside/praziquantel	1.9	95.3%

Effectiveness of an emodepside/praziquantel topical solution against immature adults of *A. tubaeforme* infections in cats is shown in the following table:

Table 10: Effectiveness of Emodepside/Praziquantel against immature adult *A. tubaeforme*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 3: placebo	76.1	n/a
Group 4: emodepside/praziquantel	1.9	97.6

Adverse Reactions: None reported.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 98.7% and 95.3% effective against fourth stage larval and 97.6% effective against immature adult *A. tubaeforme* infection in cats.

4) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Immature [Fourth Stage (L4) and Immature Adults] *Ancylostoma tubaeforme* in Cats. (Study #151.076, Report #75608)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against immature induced *A. tubaeforme* infections in the cat after one topical application

Study Investigator: Dr. Larry Cruthers

Location: Professional Laboratory and Research Services, Inc., Corapeake, NC

Animals: 32 domestic shorthair kittens (16 males and 16 females), approximately 3 months to 4 months old weighing 1.1 and 1.7 kg, 8 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 3: placebo (vehicle without active ingredients)
Group 4: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied to the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 17 days

Study Design: Cats experimentally infected with *A. tubaeforme* were randomly allocated to four groups. Groups 1 and 2 were treated on day 7 and groups 3 and 4 were treated on day 11 to target different immature stages. Following a 5-day (6-day with groups 3 and 4) post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *A. tubaeforme* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against infections with fourth stage larvae *A. tubaeforme* in cats is shown in the following table:

Table 11: Effectiveness of Emodepside/Praziquantel against fourth stage larvae *A. tubaeforme*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	14	n/a
Group 2: emodepside/praziquantel	0	100
Group 3: placebo	13.5	n/a
Group 4: emodepside/praziquantel	0	100

Effectiveness of emodepside/praziquantel topical solution against infections with immature adult *A. tubaeforme* in cats is shown in the following table:

Table 12: Effectiveness of Emodepside/Praziquantel against immature adult *A. tubaeforme*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	8.7	n/a
Group 2: emodepside/praziquantel	0	100
Group 3: placebo	27.1	n/a
Group 4: emodepside/praziquantel	0	100

Adverse Reactions: None reported

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against infections with fourth stage larvae and immature adult *A. tubaeforme* in cats.

Cestode Studies (*Taenia taeniaeformis*)

1) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Taenia taeniaeformis* Infection in Cats. (Study # 151.652, Report # 75627)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against natural *T. taeniaeformis* infections in the cat after one topical application.

Study Investigator: Dr. Dawie Kok

Location: ClinVet International, Bloemfontein, S. Africa

Animals: 20 adult mixed breed cats (5 males and 15 females), weighing 1.7 to 4.6 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied on the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 11 days

Study Design: Cats naturally infected with *T. taeniaeformis* were randomly assigned to two treatment groups. Following an 11-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *T. taeniaeformis* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against natural infections with *T. taeniaeformis* in cats is shown in the following table:

Table 13: Effectiveness of Emodepside/Praziquantel against adult *T. taeniaeformis*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	2.6	n/a
Group 2: emodepside/praziquantel	0	100

Adverse Reactions: One cat vomited 2 hours after treatment with emodepside/praziquantel topical solution.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against natural infections with *T. taeniaeformis* in cats.

2) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Taenia taeniaeformis* Infection in Cats. (Study # 151.085, Report # 75626)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against natural *T. taeniaeformis* infections in the cat after one topical application.

Study Investigator: Dr. Dwight Bowman

Location: CHK R & D, (Cheri-Hill Kennels) Stanwood, MI

Animals: 20 mixed breed adult cats (6 males and 14 females), weighing 2.5 to 7.1 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied on the skin on the neck at the base of the skull.

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats naturally infected with *T. taeniaeformis* were randomly allocated to two groups. Following a 10-day post-treatment observation period, animals were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *T. taeniaeformis* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against natural infections with *T. taeniaeformis* infections in cats is shown in the following table:

Table 14: Effectiveness of Emodepside/Praziquantel against adult *T. taeniaeformis*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	4.5	n/a
Group 2: emodepside/praziquantel	0	100

Adverse Reactions: None noted.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against natural infections with *T. taeniaeformis* in cats.

Cestode Studies (*Dipylidium caninum*)

1) Evaluation of the Efficacy of Different Dose Levels of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Dipylidium caninum* Infection in Cats. (Study # 151.601, Report # 75625)

Purpose: The study was conducted to determine the safety and effectiveness of three dose levels of emodepside and praziquantel against natural *D. caninum* infections in the cat after one topical application.

Study Investigator: Dr. Dawie Kok

Location: ClinVet International, Bloemfontein, South Africa

Animals: 40 mixed breed domestic short and longhair cats (15 males and 25 females), young adult and adult, weighing from 2.1 to 4.2 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 1.5 mg/kg emodepside and 6 mg/kg praziquantel
Group 3: 3 mg/kg emodepside and 12 mg/kg praziquantel
Group 4: 6 mg/kg emodepside and 24 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied on the skin on the neck at the base of the skull.

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats, naturally infected with *D. caninum,* were randomly allocated to four groups. Following a 10-day post-treatment observation period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *D. caninum* were recovered, identified, and counted.

Results: Effectiveness of emodepside and praziquantel against natural infection with *D. caninum* in cats is shown in the following table:

Table 15: Effectiveness of Emodepside/Praziquantel against adult *D. caninum*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effective-ness
Group 1: placebo	8.5	n/a
Group 2: 1.5 mg/kg emodepside/6 mg/kg praziquantel	1.3	84.4
Group 3: 3 mg/kg emodepside/12 mg/kg praziquantel	0	100
Group 4: 6 mg/kg emodepside/24 mg/kg praziquantel	0	100

Adverse Reactions: One cat vomited 2 hours after being dosed with the vehicle. Self-limiting conjunctivitis was seen in many of the cats in all groups within a few hours of dosing: 7 cats in groups 1 and 3, 2 in group 2, and 3 in group 4.

Conclusions: The dose of 3 mg/kg emodepside and 12 mg/kg praziquantel was 100% effective against natural infections with *D. caninum.*

2) Evaluation of the Efficacy of a Combination of BAY 44-4400 (Emodepside) and Praziquantel against Natural *Dipylidium caninum* Infection in Cats. (Study # 151.083, Report # 75617)

Purpose: The study was conducted to determine the safety and effectiveness of emodepside/praziquantel against natural *D. caninum* infections in the cat after one topical application. The study was also conducted to demonstrate non-interference of emodepside when combined with praziquantel against natural *D. caninum* infection in the cat.

Study Investigator: Dr. Larry Cruthers

Location: Professional Laboratory and Research Services, Inc (PLRS), Corapeake, NC

Animals: 40 domestic long hair and shorthair adult cats (19 males and 21 females), weighing from 1.9 to 6.4 kg, 10 per group

Treatment Groups: Group 1: placebo (vehicle without active ingredients)
Group 2: 3 mg/kg emodepside
Group 3: 12 mg/kg praziquantel
Group 4: 3 mg/kg emodepside and 12 mg/kg praziquantel

Dosage Form: Topical solution

Route of Administration: Topical, applied on the skin on the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 10 days

Study Design: Cats naturally infected with *D. caninum* were randomly allocated to four groups and treated on study day 0. Following a 10-day post-treatment period, cats were euthanized and necropsied.

Variables Measured: Cats were observed daily for local or systemic reactions to the treatment. At necropsy, the gastrointestinal tract was opened and surviving *D. caninum* were recovered, identified, and counted.

Results: Effectiveness of emodepside/praziquantel topical solution against natural infections with *D. caninum* in cats is shown in the following table:

Table 16: Effectiveness of Emodepside/Praziquantel against adult *D. caninum*

Treatment Group	Geometric Mean No. of Worms at Necropsy	Percent Effectiveness
Group 1: placebo	5.5	n/a
Group 2: emodepside alone	5.3	2.7
Group 3: praziquantel alone	0.1	98.7
Group 4: emodepside/praziquantel	0	100

Adverse Reactions: One group 4 cat died on study day 10 prior to scheduled euthanasia and necropsy. The histopathological findings were diagnostic for multifocal, chronic-active cholangiohepatitis. This was a random source cat with multiple potential causes for cholangiohepatitis. While the use of drug does not appear to be the direct cause of this cat's death, treatment with the drug cannot be ruled out as a contributing cause. The label has a precaution against use in sick or debilitated animals.

Conclusions: A single topical dose of emodepside/praziquantel topical solution was 100% effective against *D. caninum*. The praziquantel alone was 98.7% effective. The addition of emodepside did not interfere with the effectiveness of praziquantel against *D. caninum.* The emodepside showed no activity against *D. caninum.*

Field Safety and Effectiveness Study

Clinical Evaluation of the Safety and Efficacy of BAY 44-4400 (Emodepside) and Praziquantel Topical Solution against Nematode and Cestode Infections in Cats.
(Study # 151.095, Report # 75628)

Study Investigators and Locations: This was a multi-center study. Veterinarians and staff from 13 veterinary clinics, located in the USA and Canada, conducted this study.

Dr. Jan Strother, Hartselle, AL
Dr. Victor Manoharan, West Palm Beach, FL
Dr. Craig Staehle, O'Fallon, MO
Dr. Richard Mauldin, Oklahoma City, OK
Dr. Brent Husband, Wilsonville, OR
Dr. Cynthia Haas, Knoxville, TN
Dr. Laird Laurence, Fredericksburg, TX
Dr. Kenneth Brooks, Lodi, WI
Dr. Ray Snopek, Abbotsford, BC, Canada
Dr. Roger Sifferman, Springfield, MO
Dr. Liz O'Brien, Hamilton, Ontario, Canada
Dr. Donnie Gamble, Summerville, SC
Dr. Bill Campaigne, Seguin, TX

Purpose: The objective of the field study was to assess the clinical safety and effectiveness of a single topical dose of emodepside and praziquantel when administered by owners.

Animals: A total of 837 purebred or crossbred cats from 296 unique households were enrolled in this study. Seven hundred and ninety-five cats completed the study with 582 cats in the test article group and 213 cats in the active control group. A total of 606 cats treated with emodepside and praziquantel and 231 cats treated with the active control were included in the safety evaluation. A total of 312 cats from 213 households were eligible for inclusion in the effectiveness analysis (241 treated with emodepside and praziquantel, 71 with the active control).

Table 17: Effectiveness Eligibility

	Effectiveness Eligibility	Emodepside/ Praziquantel	Active Control
Total cats	312	241	71
Total households	213	167	46
T. cati eligible cats/ households	82	66	16
D. caninum eligible cats/households	142	108	34

Treatment Groups and Route of Administration:
Group 1: REVOLUTION (selamectin) topically and CESTEX (epsiprantel) oral tablets (dosed according to label directions)
Group 2: 3 mg/kg emodepside and 12 mg/kg praziquantel topically and placebo oral tablets

Frequency of Treatment: Single treatment

Duration of Study: 27 to 33 days

Study Design: Cats infected with *Toxocara cati* or *Dipylidium caninum* were randomly allocated to treatment groups by household. Topical treatments were administered by cat owners. Physical exams and fecal exams were conducted 7-15 days post-treatment. Another physical examination was conducted 27-33 days following treatment. Cats were observed by their owners at three specified intervals following treatment: 30-60 minutes, 4-6 hours, and 22-26 hours post-treatment.

Variables Measured: Treatment success for *Dipylidium caninum* was determined for each cat based on the criteria that the post-treatment fecal/segment examinations were negative for cestodes. For *Toxocara cati*, treatment success was based on reduction of fecal egg counts from pre-treatment to post-treatment. Post-treatment owner observations and veterinary examinations were used to evaluate safety.

Statistical Methods: *Dipylidium caninum*: A non-inferiority test was used to compare the treatment success rate between the two treatment groups. A one-sided lower 95% confidence interval based on the difference in success rates (test drug minus active control) was calculated. The conclusion that the test drug is non-inferior to the active control drug is made if the lower bound of the confidence interval for the differences in success rates is greater than the delta (-15%).

Toxocara cati: A statistical analysis using the sign test to compare the pre-treatment egg counts to the post-treatment egg counts for each treatment group was conducted. The conclusion that the test drug is non-inferior to the active control drug is made if the post-treatment egg counts are significantly different from the pre-treatment egg counts for each treatment group and the percent reduction in egg count for each treatment is greater than 90%

Results: *Dipylidium caninum*: The treatment success rate for the test drug was 99.1% and for the active control, 97.1%. The lower bound of the one-sided 95% confidence interval for the differences in success rates (-2.0%) was greater than the delta (-15%). The test drug was concluded to be non-inferior to the active control drug.

Toxocara cati: The tests show that the pre-treatment egg counts were significantly higher than the post-treatment egg counts in both treatment groups ($p<0.0001$). The calculated percent reduction in egg counts was 99.9% for the test drug and 100.0% for the active control. The test drug was concluded to be non-inferior to the active control drug

Adverse Reactions: All adverse reactions were self-limiting and did not require treatment. The most commonly reported adverse drug reaction associated with emodepside/praziquantel was the appearance of a stiff, sticky, white residue at the application site. This was reported 34 times and in some cases was present for up to 2

days following treatment. There were also 15 reports of an oily appearance to the treatment site following application of emodepside/praziquantel topical solution. Other adverse reactions included the following:

Table 18: Adverse Reactions in the Field Study

Emodepside/Praziquantel Adverse Reactions	No. of Cats (%) N = 606
Licking, excess grooming	18 (3.0)
Scratching at treatment site	15 (2.5)
Salivation	10 (1.7)
Lethargy	10 (1.7)
Alopecia	8 (1.3)
Agitation, nervousness	7 (1.2)
Vomiting	6 (1.0)
Diarrhea	3 (0.5)
Eye irritant	3 (0.5)
Respiratory irritant	1 (0.2)
Shaking/tremors	1 (0.2)

Conclusions: A single dose of emodepside/praziquantel topical solution when administered by owners under actual condition of use was well tolerated and effective in cats against *Toxocara cati* and *Dipylidium caninum.*

III. TARGET ANIMAL SAFETY:

A. Margin of Safety:

Evaluation of the Safety of Emodepside (BAY 44-4400) and Praziquantel Topical Solution in 8-Week-Old Kittens.
(Study # 151.090, Report # 75688)
Good Laboratory Practices (GLP) Laboratory Study

Purpose: The purpose of the study was to demonstrate the safety of emodepside/praziquantel topical solution when administered topically to kittens at 14 day intervals for 6 treatments.

Study Investigator: B. S. Wahle, MS

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 48 domestic shorthair kittens (24 males and 24 females), 7 to 7.6 weeks of age, weighing 0.5 to 0.9 kg at the time of the initial treatment, 12 kittens (6 males and 6 females) per treatment group

Treatment Groups: Kittens were treated topically with 1X, 3X and 5X multiples of the maximum 1X dose of emodepside/praziquantel.

Table 19: Dose/Treatment Groups

Treatment Group	Dose of Emodepside/Praziquantel
1	1X (0.7 mL/kg)
2	3X (2.1 mL/kg)
3	5X (3.5 mL/kg)
4	Control (vehicle at 3.5 mL/kg)

1X dose for this study = label dose volume (0.35 mL) ÷ body weight of smallest kitten in the 1X treatment group (0.5 kg).

Dosage Form: Topical solution

Route of Administration: Topical Fur was parted and the product applied topically from the base of the head to the shoulders.

Frequency of Treatment: Once every 14 days for six consecutive treatments (days 0, 14, 28, 42, 56, and 69)

Variables Measured: Clinical observations were made twice daily except on treatment days when they were made at 1, 2, 4, and 6 (± 0.5) hours post-treatment. Physical examinations were performed on days -6, 1, 35, and 69. Food consumption was measured daily. Body weights were recorded weekly. On days -5, 1, 34, and 70, serum and whole blood were collected and submitted for clinical chemistry and hematology profiles. On days -2/-1, 40/41, and 64/65, urine was collected and submitted for urinalysis. At study conclusion, kittens were euthanized and necropsied. Gross pathology and histopathology were performed.

Statistical Methods: A mixed model repeated measures analysis of covariance was conducted for each variable with baseline as the covariate. Fixed effects examined were sex, time, dosage, and the interactions sex-by-time, time-by-dosage, sex-by-dosage, and sex-by-time-by-dosage. Least square means associated with statistically significant effects were examined for clinical significance, with all interactions involving sex evaluated at the unadjusted 0.05 level of significance and with dosage and dosage-by-time evaluated at the unadjusted 0.10 level of significance.

Results: One 5X kitten experienced salivation and tremors on dosage day 0. Oral ingestion is assumed because the dose spread down its front legs. Another 5X kitten experienced salivation on dosage days 0 and 56. A third 5X kitten experienced tremors on day 1. These kittens were normal the following day. There was sporadic vomiting and soft stools reported in all groups including three kittens (one each in vehicle, 3X, and 5X groups) that vomited within 24 hours of dosing. There were no differences among the groups in physical examination findings, body weights, or food

consumption. No differences were noted between groups on necropsy or histopathology. One 5X female kitten had a soft area with thin cortex in the cranial pole of the left kidney seen grossly. Microscopically, this area corresponded to a wedged shaped area of fibrosis and mild chronic inflammation. The rest of the kidney showed no changes, toxic or otherwise, so these findings were not considered treatment-related.

Conclusions: Emodepside/praziquantel topical solution was well tolerated following topical administration to 8-week-old kittens. Clinical observations included transient, self-limiting salivation and/or tremors in three 5X kittens. Three kittens (one each in the 0X, 3X, and 5X groups) vomited within 24 hours of dosing.

B. Oral Safety:

Oral Safety Study with Emodepside and Praziquantel Topical Solution in Cats.
(Study # 151.092, Report # 75689)
GLP Laboratory Study

Purpose: To demonstrate the safety of emodepside/praziquantel topical solution when administered orally to cats at the recommended dermal unit dose.

Study Investigator: B. S. Wahle, MS

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 16 domestic shorthair cats (8 males and 8 females), approximately 7 to 8 months old, weighing 2.7 to 5.3 kg at the time of the treatment, 8 cats (4 males and 4 females) per treatment group

Treatment Groups: 1X: 0.7 mL for cats weighing > 2.5 and ≤ 5 kg
1.12 mL for cats weighing > 5 kg
Control: water, 0.7 mL

Dosage Form: Topical solution

Route of Administration: Oral

Frequency of Treatment: One dose, day 0

Variables Measured: Clinical observations were made twice daily except on treatment day when they were made at 1, 2, 4, and 6 (± 0.5) hours post-treatment. Physical examinations were performed on days -7, 1, and 17. Food consumption was measured daily. Body weights were recorded weekly. On days -7, 1, and 17, serum and whole blood were collected and submitted for clinical chemistry, hematology, and coagulation profiles. On days -4/-3, 8/9, and 15/16, urine was collected and submitted for urinalysis.

Statistical Methods: A mixed model repeated measures analysis of covariance was conducted for each variable with baseline as the covariate. Fixed effects examined were sex, time, dosage, and the interactions sex-by-time, time-by-dosage, sex-by-dosage, and sex-by-time-by-dosage. Least square means associated with statistically significant effects were examined for clinical significance, with all interactions involving sex evaluated at the unadjusted 0.05 level of significance and with dosage and dosage-by-time evaluated at the unadjusted 0.10 level of significance.

Results: Mild, transient signs (salivation in six cats and vomiting in two cats) were observed post-treatment in cats in the 1X group. Results of physical examinations were unremarkable. While there was no statistical difference between the groups for weekly mean food consumption, examination of daily intake showed that the 1X group had decreased food consumption for several days after treatment. This was particularly evident on day 1 when the control group's mean was 68.7 grams (g) compared to 22.8 g for the 1X group. The 1X group also experienced weight loss. On day 7, the 1X group mean weight (3,768 g) was lower than at the start of the study (3,907 g). There was a statistical difference in overall weight between the two groups ($p = 0.086$). The 1X cats did start to regain the weight by the end of the study. There were no clinically significant differences between groups in chemistry, hematology, and urinalysis indices.

Conclusions: Oral exposure to emodepside/praziquantel topical solution caused salivation and vomiting. Oral exposure also caused transient decreased food consumption and weight loss.

Emodepside (1.98%, w/w) and Praziquantel (7.94%, w/w) Topical Solution: Pilot Oral Safety Study in 8 to 12-Month-Old Cats.
(Report # 75166)

Purpose: The purpose of the study was to provide preliminary information regarding the safety of an investigational new animal drug (emodepside and praziquantel topical solution) when administered orally to cats at the recommended dermal unit dose (1X).

Study Investigator: R. E. Mueller, MS

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 16 domestic shorthair cats (8 males and 8 females), approximately 8 to 12 months old, weighing 3.0 to 4.8 kg at the time of the treatment, 8 cats (4 males and 4 females) per treatment group

Treatment Groups: 1X: 0.7 mL
Control: vehicle (formulation minus the two active ingredients), 0.7 mL

Dosage Form: Topical solution

Route of Administration: Oral

Frequency of Treatment: One dose, day 0

Variables Measured: Clinical observations were made before and at multiple times post-treatment on the day of treatment. Beginning with the day of treatment, food consumption was measured daily. Body weights were recorded weekly. On days -4, 1 and 7, blood was collected and submitted for clinical chemistry, hematology, and coagulation parameters (no coagulation parameters were done on day -4). Physical examinations were performed on day 14.

Results: After oral dosing, all cats salivated and four cats, two in each group, vomited. Two to four hours after dosing, tremors (two cats), abnormal gait (one cat), and abnormal respiration (one cat) were observed in the 1X group. These clinical signs resolved without treatment.

Conclusions: The oral administration of emodepside/praziquantel topical solution to young adult cats induced salivation, vomiting, tremors, abnormal gait and abnormal respiration.

C. Dose Tolerance:

Dose Tolerance Study with Emodepside (Bay 44-4400) and Praziquantel Topical Solution in the Cat.
(Study # 151.093, Report # 75690)
GLP Laboratory Study

Purpose: To demonstrate the safety of emodepside/praziquantel topical solution at 10 times the unit dosage in cats.

Study Investigator: B. S. Wahle, MS

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 16 domestic shorthair cats (8 males and 8 females), approximately 7 to 8 months of age, weighing 2.4 to 5.1 kg at the time of the treatment, 8 cats (4 males and 4 females) per treatment group

Treatment Groups: 10X: 3.5 mL for cats weighing ≤ 2.5 kg
7.0 mL for cats weighing > 2.5 kg and ≤ 5 kg
11.2 mL for cats weighing > 5 kg

Control: vehicle (formulation minus the two active ingredients) at 10X as above

Dosage Form: Topical solution

Route of Administration: Topical

Frequency of Treatment: One dose, day 0

Variables Measured: Clinical observations were made before and at multiple times post-treatment on the treatment day. Physical examinations were performed on days -7, 1, and 28. Food consumption was measured daily. Body weights were recorded weekly. On days -7, 1, and 25, serum and whole blood were collected and submitted for clinical chemistry, hematology, and coagulation profiles. On days -4/-3, 8/9, and 24/25, urine was collected and submitted for urinalysis.

Statistical Methods: A mixed model repeated measures analysis of covariance was conducted for each variable with baseline as the covariate. Fixed effects examined were sex, time, dosage, and the interactions sex-by-time, time-by-dosage, sex-by-dosage, and sex-by-time-by-dosage. Least square means associated with statistically significant effects were examined for clinical significance, with all interactions involving sex evaluated at the unadjusted 0.05 level of significance and with dosage and dosage-by-time evaluated at the unadjusted 0.10 level of significance.

Results: One vehicle-treated and two 10X cats salivated after dosing. One 10X cat had tremors and was lethargic after dosing. Clinical signs resolved within about 48 hours after dosing. The skin at the site of application was normal, although the fur appeared clumped temporarily. There was no statistical difference between treatment groups in daily food consumption and mean body weights increased slightly in both groups.

Conclusions: The topical administration of emodepside/praziquantel topical solution, one time at 10X the recommended label dose volume caused self-limiting salivation, tremors and lethargy.

D. Heartworm Safety:

Evaluation of the Safety of Emodepside and Praziquantel Topical Solution in Heartworm Positive Cats.
(Study # 151.362, Report # 75660 and 75660-1)
GLP Laboratory Study

Purpose: To demonstrate the safety of emodepside/praziquantel topical solution administered topically, at 1X and 5X the recommended dose once a month for 3 months, to cats artificially infected with adult heartworms, *Dirofilaria immitis*.

Study Investigator: B. S. Wahle, MS

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 36 domestic shorthair cats (18 males and 18 females), 8 to 11 months of age, weighing 2.1 to 4.9 kg at the time of the initial treatment, 12 cats (6 males and 6 females) per treatment group On study day -21, six adult heartworms (three females and three males) were collected from dogs and surgically transplanted into the left jugular vein of each cat to establish artificial infections.

Treatment Groups:
1X: 0.4 to 1.0 mL [Dose range: 13.7 to 22.2 mg/kg praziquantel and 3.5 to 5.7 mg/kg emodepside]
5X: 1.8 to 4.5 mL [Dose range: 64.9 to 111.4 mg/kg praziquantel and 16 to 27.8 mg/kg emodepside]
Control: mineral oil, 5X volume

Dosage Form: Topical solution

Route of Administration: Topical

Frequency of Treatment: Three doses (days 0, 28, and 56)

Variables Measured: Clinical observations were made twice daily except on treatment days when they were made at 1, 2, 4, and 6 (± 0.5) hours post-treatment. Physical examinations were performed on days -8, 1, 29, and 57. Food consumption was measured daily. Body weights were recorded weekly. On days -12, -5, 1, 29, and 57, serum and whole blood were collected and submitted for clinical chemistry, hematology, coagulation profiles, microfilarial examination, and heartworm serology. On days -13, -6, 6, 34, and 61, urine was collected and submitted for urinalysis. At study conclusion, cats were euthanized and necropsied. Live heartworms, dead heartworms, and heartworm fragments were recovered and counted. Heart and lungs from the cats that died during the study were examined histologically to determine cause of death.

Statistical Methods: The mean number of live heartworms at necropsy of cats surviving to end of study was analyzed using a generalized linear model analysis of variance with poisson distribution and log link.

Results: One 1X and three 5X cats salivated on the first day of dosing. One 5X cat had labored breathing and lethargy after the first dose. Several cats in all dose groups also had labored breathing. There were sporadic reports of vomiting and soft stool, not necessarily related to the treatment. Four cats died during the study. One cat died before receiving any treatment. One cat in the control group died 8 days following its first treatment with mineral oil. Two cats in the 5X group became moribund following the second treatment and were euthanized. Post mortem examination revealed pulmonary lesions that were consistent with feline heartworm disease as the cause of severe illness or death. All surgically transplanted adult heartworms were recovered alive and intact from these four cats at necropsy.

The number of cats surviving to the end of the study was 11 of 12 for the 0X group, 12 of 12 for the 1X group, and 10 of 12 for the 5X group. Overall, dosage was found to affect the mean number of heartworms recovered per cat ($p = 0.004$). There were fewer live heartworms recovered in the cats in the 1X and 5X groups compared to the control group.

Table 20: Mean number of live heartworms recovered from cats surviving to the end of the study.

Treatment Group (n=number of cats)	Mean number of live worms recovered at necropsy
0X (n = 11)	2.6
1X (n = 12)	1.1
5X (n = 10)	0.7

Conclusions: Emodepside/praziquantel topical solution caused salivation in the 1X and 5X groups. One 5X cat had labored breathing and was lethargic 24 hours after the first dose. Several other cats in all dose groups had labored breathing that may have been caused by the stress of handling or heartworm disease or both. The cats treated with emodepside/praziquantel had fewer live heartworms recovered at necropsy compared to the untreated cats. This study supports inclusion of precautions on the label regarding use in heartworm positive cats.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PROFENDER Topical Solution:

Human Warnings are provided on the product label as follows:
"**Not for human use. Keep out of the reach of children.**
To prevent accidental ingestion of the product, children should not come in contact with the application site for twenty-four (24) hours while the product is being absorbed. Pregnant women, or women who may become pregnant, should avoid direct contact with, or wear disposable gloves when applying, this product. Studies performed in rats and rabbits suggest that emodepside may interfere with fetal development in those species.

PROFENDER Topical Solution may be irritating to skin and eyes. Reactions such as facial, tongue and hand swelling have been reported in humans in rare instances. Avoid contact with the application area while it is wet and wash hands thoroughly with soap and warm water after handling. People with known hypersensitivity to butylhydroxyanisole, emodepside, or praziquantel should administer the product with caution. If the product accidentally gets into eyes, flush thoroughly with water. May be harmful if swallowed. In case of accidental ingestion or if skin or eye irritation occurs, call a poison control center or physician for treatment advice.

The Material Safety Data Sheet (MSDS) provides additional occupational safety information. For customer service or to obtain product information, including the MSDS, call 1-800-633-3796. For medical emergencies or to report an adverse reaction, call 1-800-422-9874.

The bolded human warning above was based on Human Risk Assessment determinations. The risk assessment estimated the potential human (adult and toddler) acute and chronic dermal and toddler hand-to-mouth oral exposure levels and levels of concern from contact with a treated cat. The risk assessment factors pet surface-to-human transfer dose, dermal absorption, and No Observable Adverse Effect Levels (NOAEL) were derived from data for emodepside and praziquantel in toxicity or pharmacokinetic studies in laboratory animals and cotton glove-stroking (drug recovery) studies in cats.

VI. 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. The data demonstrate that PROFENDER Topical Solution, when used according to the label, is safe and effective for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to monitor the safe use of the product.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

U.S. Patent Number	Date of Expiration
5 514 773	May 7, 2013
5 589 503	January 4, 2015

VII. ATTACHMENTS:

Facsimile Labeling:

- Package Insert
- Tube Labels (0.35 mL, 0.75 mL, 1.12 mL)
- Backing for Blister Packs (0.35 mL, 0.75 mL, 1.12 mL)
- Multiple Cartons (Display Cartons) (0.35 mL, 0.75 mL, 1.12 mL)
- Shipper Labels (0.35 mL, 0.75 mL, 1.12 mL)