

Date of Approval:

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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

2007-141-275

FOIS 1

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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:

$$\% \text{ Effectiveness} = (N2 - N1)/N2 \times 100$$

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 Effectiveness
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
<i>T. cati</i> eligible cats/ households	82	66	16
<i>D. caninum</i> 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

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>U.S. Patent Number</u>	<u>Date of Expiration</u>
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)

profender[®]

Topical Solution

(emodepside + praziquantel)

01289328, R.0

Contents : 8 X 24 X 1.12 mL Tubes

03615042

Auftrag: - 1

Lot:

Exp:



Bayer HealthCare

Manufactured for:
Bayer HealthCare LLC
Animal Health Division
Shawnee Mission, KS 66201
Made in Germany

Store at or below 77°F
(25°C). Protect from
freezing.

Profender® Topical Solution
(emodepside/praziquantel)
1.12 mL Shipper Label

profender[®]

Topical Solution

01289298, R.0

(emodepside + praziquantel)

Contents : 8 X 40 X 0.70 mL Tubes

03615034

Auftrag: - 1

Lot:

Exp:



Bayer HealthCare

Manufactured for:
Bayer HealthCare LLC
Animal Health Division
Shawnee Mission, KS 66201
Made in Germany

Store at or below 77°F
(25°C). Protect from
freezing.

**Profender[®] Topical Solution
(emodepside/praziquantel)
0.7 mL Shipper Label**

profender®

Topical Solution

01289182, R.0

(emodepside + praziquantel)

Contents : 8 X 40 X 0.35 mL Tubes

03615026

Auftrag: - 1

Lot:

Exp:



Bayer HealthCare

Manufactured for:
Bayer HealthCare LLC
Animal Health Division
Shawnee Mission, KS 66201
Made in Germany

Store at or below 77°F
(25°C). Protect from
freezing.

Profender® Topical Solution
(emodepside/praziquantel)
0.35 mL Shipper Label

**Profender® Topical Solution
(emodepside/praziquantel)**

**1.12 mL Multiple Carton
Panel 3 & 4**



convenient, easy to apply 

Topical Solution
profender®
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections.

**Large
For Cats and Kittens**
8 weeks of age and older
and weighing > 11 - 17.6 lbs.

Contains 24 - 1.12 ml tubes

Each tube contains 24 mg of emodepside and 96.1 mg of praziquantel.

 **Bayer**

NADA 141-275, Approved by FDA

convenient, easy to apply 

Topical Solution
profender®
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

**Large
For Cats and Kittens**
8 weeks of age and older
and weighing > 11 - 17.6 lbs.

Contains 24 - 1.12 ml tubes

Do not dispense dose applicator without complete safety and administration information.

 **Bayer**

Panel 3

Panel 4

**Profender® Topical Solution
(emodepside/praziquantel)**

**1.12 mL Multiple Carton
Panels 1 & 2 & Top Flap**



Top flap

(emodepside/praziquantel)
profender®
Topical Solution

Topical Solution
profender®
(emodepside/praziquantel)

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.

See package insert for complete product information.

Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas 66201 USA. Made in Germany.
Bayer, the Bayer Cross, and Profender are trademarks of Bayer.



Lot No.:

Exp.:

Universal Graphics

375 Morgan Lane • Suite #203 • West Haven, CT 06516
Phone: (203) 934-4275 • Fax: (203) 934-4324

File Name: Profender Display Carton 1.12 mL - 03615042_R.0

Date: 3/23/07, 4/16/07, 4/17/07, 4/9/07, 5/2/07, 5/30/07 (2), 6/1/07

Control #: 13325, 13362, 13365, 13371, 13395, 13448, 13451, 13454

Size: 190 mm x 130 mm x 115 mm

Colors: CMYK

Proof: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

HUMAN WARNINGS:

Not for human use. Keep out of 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.

PRECAUTIONS:

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See product insert ANIMAL SAFETY.)

STORAGE INFORMATION:

Store at or below 77°F (25°C). Protect from freezing.



© 2007 Bayer HealthCare LLC
03615042 R.0

Panel 2

Panel 1

**Profender® Topical Solution
(emodepside/praziquantel)**

1.12 mL Multiple Carton

az14893

Top flap



Universal Graphics	
File Name	Profender Duplici Carton 1.12 mL (08/10/07) R.D.
Date	3/23/07 4:18:07 AM 4/17/07 4:46:07 AM 5/29/07 5:59:07 PM 6/16/07
Scale	8 13325 13362 13385 13371 13395 13448 13451 13457
Size	100 mm x 130 mm x 115 mm
Colors	CMYK
Prod.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15



Topical Solution
profender.
(emodepside/praziquantel)

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.

See package insert for complete product information.

Bayer
Lot No.:
Exp:

Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas 66201 USA. Made in Germany.
Bayer, the Bayer Cross, and Profender are trademarks of Bayer.

Panel 1

HUMAN WARNINGS:
Not for human use. Keep out of 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 benzothiazopyridone, 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 1-800-422-5874.

PRECAUTIONS:
Safe use of the product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.
Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See product insert **ANIMAL SAFETY**.)

STORAGE INFORMATION:
Store at or below 77°F (25°C). Protect from freezing.

Bayer
© 2007 Bayer HealthCare LLC
03615042 R.D.

Panel 2

convenient, easy to apply

Topical Solution
profender.
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.
Topical Solution for the treatment and control of roundworm, roundworm and tapeworm infections.
Larger For Cats and Kittens 8 weeks of age and older and weighing > 11.17 lb (5 kg)
Contains 24 - 1.12 mL tubes

Bayer

Each tube contains 24 mg of emodepside and 10 mg of praziquantel.

Panel 3

convenient, easy to apply

Topical Solution
profender.
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.
Larger For Cats and Kittens 8 weeks of age and older and weighing > 11.17 lb (5 kg)
Contains 24 - 1.12 mL tubes

Bayer

Do not dispense dose applicator without complete safety and administration information.

Panel 4

az14893
130 x 115 mm
Profender

Edelmann
Stanzvorlage

**Profender® Topical Solution
(emodepside/praziquantel)**

**0.7 mL Multiple Carton
Panel 3 & 4**



convenient, easy to apply 

Topical Solution
profender®
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.
Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections.

8 weeks of age and older
and weighing > 5.5 - 11 lbs.

Contains 40 - 0.70 ml tubes

Each tube contains 15 mg of emodepside
and 60.1 mg of praziquantel.

NADA 141-275, Approved by FDA

 Bayer

convenient, easy to apply 

Topical Solution
profender®
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

8 weeks of age and older
and weighing > 5.5 - 11 lbs.

Contains 40 - 0.70 ml tubes

Do not dispense dose applicator without complete safety and administration information.

 Bayer

Panel 3

Panel 4

Top flap

**Profender® Topical Solution
(emodepside/praziquantel)**

**0.7 mL Multiple Carton
Panels 1 & 2 & Top Flap**



profender®
Topical Solution
(emodepside/praziquantel)

Topical Solution
profender®
(emodepside/praziquantel)

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.

See package insert for complete product information.

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Bayer, the Bayer Cross, and Profender are trademarks of Bayer.



Lot No.:

Exp.:



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03615034 R.0

Universal Graphics

375 Morgan Lane • Suite #203 • West Haven, CT 06516
Phone: (203) 934-4275 • Fax: (203) 934-4324

File Name: Profender Display Carton .70 mL - 03615034, R.0

Date: 3/23/07, 4/16/07, 4/17/07, 4/19/07, 4/24/07, 5/2/07, 5/30/07 (2), 6/1/07

Control #: 13324, 13361, 13364, 13370, 13384, 13394, 13447, 13450, 13453

Size: 190 mm x 103 mm x 115 mm

Colors: CMYK

Proof: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

ADDITIONAL WARNINGS:

Profender Topical Solution is a prescription drug. It is intended for use in cats only. Do not use in dogs, horses, or other animals. 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.

PRECAUTIONS:

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See product insert **ANIMAL SAFETY**.)

STORAGE AND HANDLING:

Store at or below 77°F (25°C). Protect from freezing.

Panel 1

Panel 2

**Profender® Topical Solution
(emodepside/praziquantel)**

0.7 mL Multiple Carton

Top Flap



<i>Universal Graphics</i>	
<small>1775 Morgan Lane • Suite 200 • West Haven, CT 06457 Phone: (203) 431-1221 • Fax: (203) 431-1221</small>	
File Name: Profender Display Carton 70 ml - 03615034_R10	
Date: 1/21/07 4:18:07 4:17:07 4:18:07 4:24:07 3:27:07 3:28:07 (2) 6:11:07	
Control #: 13324 13381 13384 13370 13384 13384 13447 13450 13485	
Size: 190 mm x 103 mm x 115 mm	
Color: CMYK	
Proof: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	

Topical Solution
profender
(emodepside/praziquantel)

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 taenaeformis* (adults) in cats.

See package insert for complete product information.

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Bayer
Lot No.:
Exp.:

Bayer
© 2007 Bayer HealthCare LLC
03615034 R10

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.

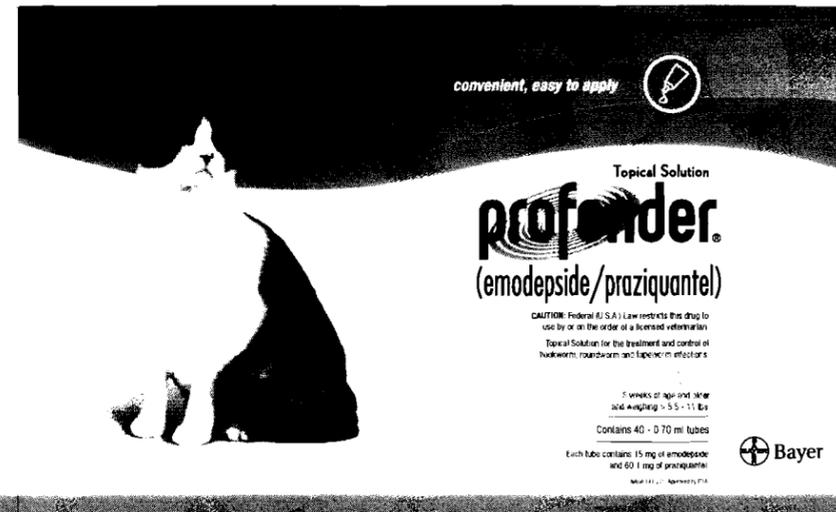
PROFENDER Topical Solution may be irritating to skin and eyes. Reactions such as facial, tongue and hand swelling have been reported in humans in rare instances. Avoid contact with the application site while it is wet and wash hands thoroughly with soap and warm water after handling. People with known 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.

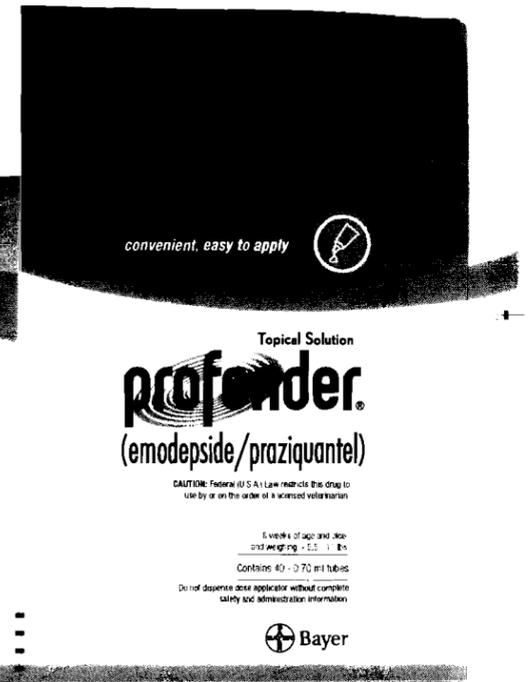
Safe use of this product has not been evaluated in cats less than 6 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See product insert **ANIMAL SAFETY**.)

Store at or below 77°F (25°C). Protect from freezing.



Panel 3



Panel 4

m1591206
190 x 103 x 115 mm
Profender

Edelmann
 Stanzvorläge

**Profender® Topical Solution
(emodepside/praziquantel)**

**0.35 mL Multiple Carton
Panel 3 & 4**

convenient, easy to apply 

Topical Solution
profender®
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections.

8 weeks of age and older and weighing at least 2.2-5.5 lbs.

Contains 40 - 0.35 ml tubes

Each tube contains 7.5 mg of emodepside and 30 mg of praziquantel.

NADA 141-215, Approved by FDA

 Bayer

convenient, easy to apply 

Topical Solution
profender®
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

8 weeks of age and older and weighing at least 2.2-5.5 lbs.

Contains 40 - 0.35 ml tubes

Do not dispense dose applicator without complete safety and administration information.

 Bayer

Panel 3

Panel 4

Top Flap

**Profender® Topical Solution
(emodepside/praziquantel)**

**0.35 mL Multiple Carton
Panels 1 & 2 & Top Flap**



Universal Graphics

375 Morgan Lane • Suite #203 • West Haven, CT 06516
Phone: (203) 934-4275 • Fax: (203) 934-4324

File Name: Profender Display Carton .35 mL - 03615026, R.0

Date: 3/23/07, 4/16/07, 4/17/07, 4/19/07, 4/24/07, 5/2/07, 5/30/07 (2), 6/1/07

Control #: 13323, 13360, 13363, 13369, 13383, 13383, 13446, 13449, 13452

Size: 190 mm x 103 mm x 115 mm

Colors: CMYK

Proof: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

(emodepside/praziquantel)
Profender®
Topical Solution

Topical Solution
Profender®
(emodepside/praziquantel)

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.

See package insert for complete product information.

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Lot No.:

Exp.:



© 2007 Bayer HealthCare LLC
03615026 R.0

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.

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See product insert **ANIMAL SAFETY**.)

Store at or below 77°F (25°C). Protect from freezing.

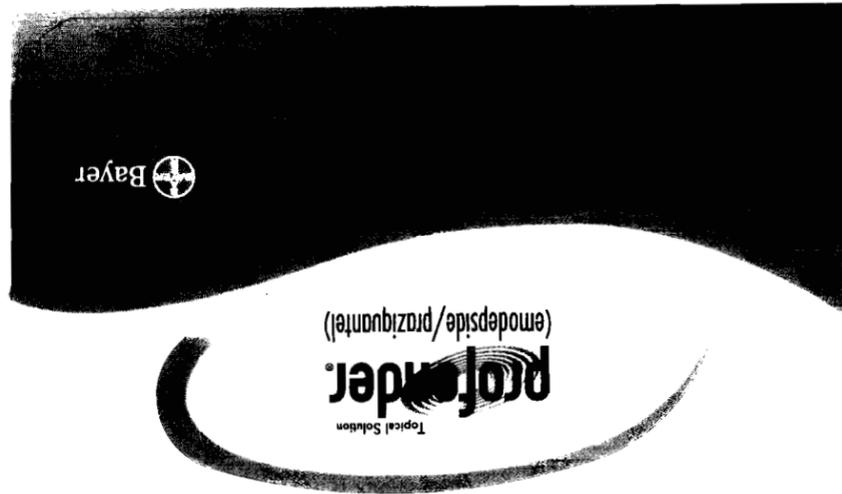
Panel 1

Panel 2

**Profender® Topical Solution
(emodepside/praziquantel)**

0.35 mL Multiple Carton

Top flap



Universal Graphics	
File Name:	Profender-Original-Carton_35 ml - 03615026_R 0
Date:	12/17/11 11:01:43 AM 4/17/12 4/17/12 4/17/12 4/17/12 4/17/12
Device:	8 100x 103x 115mm 100x 103x 115mm 100x 115mm 100x 115mm
Size:	100 mm x 103 mm x 115 mm
Color:	CMYK
Print:	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Topical Solution
profender.
(emodepside/praziquantel)

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.

See package insert for complete product information.

Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas 66201 USA. Made in Germany.
Bayer, the Bayer Cross, and Profender are trademarks of Bayer.



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.

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.
Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See product insert ANIMAL SAFETY.)

Store at or below 77°F (25°C). Protect from freezing.

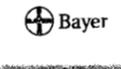


Topical Solution
profender.
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.
Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections.

8 weeks of age and older and weighing at least 2.2-5.5 lbs.
Contains 40 - 0.35 ml tubes

Each tube contains 7.5 mg of emodepside and 10 mg of praziquantel.



Topical Solution
profender.
(emodepside/praziquantel)

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

8 weeks of age and older and weighing at least 2.2-5.5 lbs.
Contains 40 - 0.35 ml tubes

Do not dispense dose applicator without complete safety and administration information.



Panel 1

Panel 2

Panel 3

Panel 4

m1591206
190 x 103 x 115 mm
Profender

Edelmann
Stanzvorläge

**Profender® Topical Solution
(emodepside/praziquantel)**

0.35 mL Tube Label



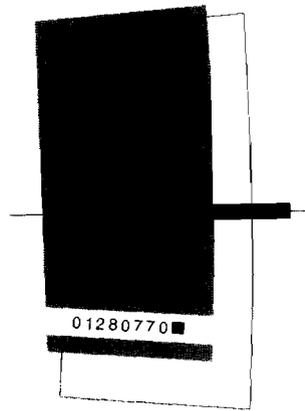
Profender® Topical Solution
(emodepside/praziquantel)

0.7 mL Tube Label



**Profender® Topical Solution
(emodepside/praziquantel)**

1.12 mL Tube Label



**Profender® Topical Solution
(emodepside/praziquantel)**

0.35 mL Blister

Topical Solution
profender.
(emodepside/praziquantel)

(7.5 mg emodepside + 30 mg praziquantel)

Small

For cats and kittens 2.2-5.5 lbs

0.35 mL

03615026, R.0



01281041

Store at or below 77°F (25°C). Protect from freezing.

See package insert for safety and administration information prior to use.

Made in Germany. Bayer, the Bayer Cross and Profender are trademarks of Bayer.

LOT and EXP: see stamp printing

Topical Solution
profender.
(emodepside/praziquantel)

(7.5 mg emodepside + 30 mg praziquantel)

Small

For cats and kittens 2.2-5.5 lbs

0.35 mL

03615026, R.0



01281041

Store at or below 77°F (25°C). Protect from freezing.

See package insert for safety and administration information prior to use.

Made in Germany. Bayer, the Bayer Cross and Profender are trademarks of Bayer.

LOT and EXP: see stamp printing

Topical Solution
profender.
(emodepside/praziquantel)

(7.5 mg emodepside + 30 mg praziquantel)

Small

For cats and kittens 2.2-5.5 lbs

0.35 mL

03615026, R.0



01281041

Store at or below 77°F (25°C). Protect from freezing.

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LOT and EXP: see stamp printing

**Profender® Topical Solution
(emodepside/praziquantel)**

0.7 mL Blister

Topical Solution
profender.
(emodepside/praziquantel)

(15 mg emodepside + 60.1 mg praziquantel)

Medium

For cats and kittens > 5.5 - 11 lbs.

0.70 mL

03615034, R.0



01281076

Store at or below 77°F (25°C). Protect from freezing.
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03615034, R.0



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0.70 mL

03615034, R.0



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LOT and EXP. see stamp printing

**Profender® Topical Solution
(emodepside/praziquantel)**

1.12 mL Blister

Topical Solution
profender.
(emodepside/praziquantel)

(24 mg emodepside + 96.1 mg praziquantel)

Large

For cats > 11-17.6 lbs

1.12 mL

03615042, R.0

01280800

Store at or below 77°F (25°C). Protect from freezing.
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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.

PRECAUTIONS:

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.2 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See ANIMAL SAFETY.)

ADVERSE REACTIONS:

Field study: In a controlled, double-masked field safety study, owners administered PROFENDER Topical Solution to 606 cats. Adverse reactions reported by the cat owners included licking/excessive grooming in 18 cats (3.0%), scratching treatment site in 15 cats (2.5%), salivation in 10 cats (1.7%), lethargy in 10 cats (1.7%), alopecia in 8 cats (1.3%), agitation/nervousness in 7 cats (1.2%), vomiting in 6 cats (1.0%), diarrhea in 3 cats (0.5%), eye irritation in 3 cats (0.5%), respiratory irritation in 1 cat (0.2%) and shaking/tremors in 1 cat (0.2%). All adverse reactions were self-limiting.

Laboratory effectiveness studies: One cat died 10 days after receiving PROFENDER Topical Solution. The necropsy showed chronic active cholangiohepatitis. While the use of the drug did not appear to be the direct cause of death, treatment with the drug cannot be ruled out as a contributing factor (See PRECAUTIONS). One cat treated with a vehicle placebo (formulation minus the active ingredients) showed salivation, gagging, lethargy and a swollen tongue.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in foreign markets: application site reaction (hair loss, dermatitis, pyoderma, edema, and erythema), salivation, pruritus, lethargy, vomiting, diarrhea, dehydration, ataxia, loss of appetite, facial swelling, rear leg paresis, seizures, hyperesthesia, twitching, and death.

EFFECTIVENESS:

In a total of 13 controlled laboratory studies to establish effectiveness, 149 cats were treated with PROFENDER Topical Solution. In the field study conducted at 13 veterinary clinics/hospitals, 837 purebred or crossbred cats from single and multi-cat households were enrolled to evaluate safety and effectiveness under field conditions of use. Of those, 606 received a single treatment with PROFENDER Topical Solution. Cats ranged in age between 2 months and 17 years and weighed between 0.8 lbs (0.36 kg) and 21 lbs (9.62 kg). Data from these studies demonstrated PROFENDER

Topical Solution 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).

ANIMAL SAFETY:

In a field study, PROFENDER Topical Solution was used in cats receiving other frequently used products including: analgesics, anti-fungals, non-steroidal anti-inflammatories, anthelmintics, antimicrobials, flea and tick products, sedatives, anesthetics, cardiac medications, anxiolytics, hormonal treatments, steroids, otic and ophthalmic preparations, and vaccines.

Dose Tolerance Study in Cats: PROFENDER Topical Solution was applied topically one time to young cats at 10X the recommended label use rate. Two cats salivated. Another cat exhibited tremors and lethargy. These signs were self-limiting.

Oral Safety Studies in Cats: PROFENDER Topical Solution was administered orally at the recommended topical dose to young adult cats. The cats exhibited salivation, vomiting, tremors, abnormal gait, abnormal respiration and weight loss. These signs were self-limiting.

General Safety Study in Kittens: PROFENDER Topical Solution was topically applied at 0X (vehicle control), 1X, 3X and 5X the maximum dose to 48 healthy 8-week-old kittens every two weeks for six doses. One 5X kitten experienced salivation and tremors and another 5X kitten experienced salivation on the day of dosing. A third 5X kitten experienced tremors the day after dosing. Three cats vomited within 24 hours of dosing, one each in vehicle control, 3X and 5X groups.

Safety Study in Heartworm Positive Cats: Cats artificially infected with adult heartworms harvested from dogs were treated topically with PROFENDER Topical Solution at 0X, 1X or 5X the recommended dose once a month for three treatments. Clinical signs included salivation (one 1X and three 5X cats), labored breathing (all groups) and lethargy (one 5X cat). At the study conclusion, the 1X and 5X cats had fewer live heartworms recovered than the 0X group.

STORAGE INFORMATION:

Store at or below 77°F (25°C).
Protect from freezing.

HOW SUPPLIED:

Code Number	Applications per Package
03615026	40 - 0.35 mL tubes (10 blisters of 4 tubes)
03615034	40 - 0.70 mL tubes (10 blisters of 4 tubes)
03615042	24 - 1.12 mL tubes (6 blisters of 4 tubes)

Profender is protected by the following U.S. Patents: 5 514 773, 5 589 503, and other patents pending.

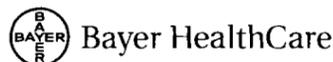
Made in Germany

NAIDA 141-275, Approved by FDA

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03615026/03615034/03615042, R.0
April, 2007



Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66201 U.S.A.



Topical Solution

profender®

(emodepside/praziquantel)

CAUTION: Federal law (U.S.A.) restricts this drug to use by or on the order of a licensed veterinarian.

Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections in cats and kittens that are at least 8 weeks of age and weigh at least 2.2 lbs (1 kg).

DESCRIPTION:

PROFENDER [1.98% emodepside/7.94% praziquantel] Topical Solution is a clear yellow ready-to-use solution packaged in single unit dosing applicator tubes for topical (dermal) treatment of cats 8 weeks of age and older and weighing at least 2.2 lbs (1 kg). The formulation and dosage schedule is designed to provide a minimum of 1.36 mg/lb (3 mg/kg) emodepside and 5.45 mg/lb (12 mg/kg) praziquantel based on body weight. Emodepside, a semi-synthetic molecule, is a cyclic depsipeptide. The chemical name is Cyclo [D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl-D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl]. Praziquantel is an isoquinoline cestocide. The chemical name is 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazine-2,1-a-isoquinoline-4-one.

INDICATIONS:

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.

DOSAGE AND ADMINISTRATION:

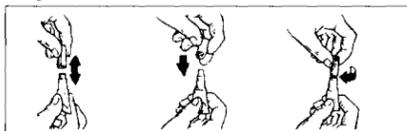
The recommended minimum dose is 1.36 mg/lb (3 mg/kg) emodepside + 5.45 mg/lb (12 mg/kg) praziquantel as a single topical dose. A single treatment is effective and a second treatment should not be necessary. If re-infection occurs, the product can be re-applied after 30 days.

1. Select the package that correctly corresponds with the body weight of the cat. (See Table below.)

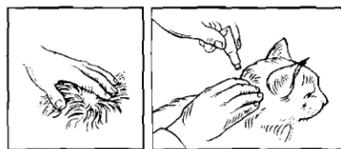
Cat Weight*	Profender Topical Solution	Volume (mL)	Emodepside (mg)	Praziquantel (mg)
2.2-5 lbs	Small	0.35	7.5	30.0
>5.5-11 lbs	Medium	0.70	15.0	60.1
>11-17.6 lbs	Large	1.12	24.0	96.1

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

2. Remove one unit dose tube from the package.
3. While holding the tube in an upright position, remove the cap from the tube.
4. Turn the cap over and place the other end of cap onto the tip of the tube.
5. Twist the cap to break the seal and then remove cap from the tube.



6. Part the hair on the back of the cat's neck at the base of the head, until the skin is visible.



7. To ensure the entire contents of the tube are administered, place the tip of the tube on the skin and squeeze the entire contents directly onto the skin. Lift tube away from the skin before releasing pressure on the tube.

Do not apply to broken skin or if hair coat is wet. Do not get this product in the cat's mouth or eyes or allow the cat to lick the application site for one hour. Oral exposure can cause salivation and vomiting. Treatment at the base of the head will minimize the opportunity for ingestion while grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.

Stiff hair, a damp appearance of the hair, or a slight powdery residue may be observed at the treatment site. These effects are temporary and do not affect the safety or effectiveness of the product.

HUMAN WARNINGS:

Not for human use. Keep out of 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.

 Bayer HealthCare

Profender® Topical Solution
(emodepside/praziquantel)

Multiple Insert
Front Panel

