Approval Date: April 17, 2003

FREEDOM OF INFORMATION SUMMARY

NADA 141-214

Zimecterin® Gold (Ivermectin/Praziquantel) Oral Paste
Anthelmintic for Horses

Merial Limited
Bldg. 500
3239 Satellite Blvd.
Duluth, GA USA 30096-4640

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Freedom of Information Summary

1. GENERAL INFORMATION:

a. NADA Number:	NADA 141-214
b. Sponsor:	Merial Limited Bldg. 500 3239 Satellite Blvd. Duluth, GA 30096-4640 USA Drug labeler code: 050604
c. Established Name:	Ivermectin/praziquantel
d. Proprietary Name:	Zimecterin® Gold Paste
e. Dosage Form:	A paste containing ivermectin 1.55% plus praziquantel 7.75%
f. How Supplied:	Individual dose syringe contains sufficient paste to treat one 1250 lb horse orally. Each weight marking on the syringe plunger delivers enough paste to treat 250 lb body weight.
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Each syringe contains 113.8 mg of ivermectin and 567.5 mg praziquantel
i. Route of Administration:	Oral
j. Species/Class:	Equine
k. Recommended Dosage:	91 mcg ivermectin per lb (200 mcg/kg) bodyweight and 454 mcg praziquantel per lb (1.0 mg/kg) bodyweight
l. Pharmacological Category:	Anthelmintic
m. Indications:	For treatment and control of the following parasites in horses:

Tapeworms:

Anoplocephala perfoliata

Large strongyles (adults):

Strongylus vulgaris (also early forms in blood vessels)
Strongylus edentatus (also tissue stages)
Strongylus equinus

Triodontophorus spp. including:
Triodontophorus brevicauda
Triodontophorus serratus

Craterostomum acuticaudatum

Small strongyles: Including those resistant to some benzimidazole class compounds (adults and 4th stage larvae)

Coronocyclus spp. including:
Coronocyclus coronatus
Coronocyclus labiatus
Coronocyclus labratus

Cyathostomum spp. including:
Cyathostomum catinatum
Cyathostomum pateratum

Cylicocyclus spp. including:
Cylicocyclus insigne
Cylicocyclus leptostomum
Cylicocyclus nassatus
Cylicocyclus brevicapsulatus

Cylicodontophorus spp.

Cylicostephanus spp. including:
Cylicostephanus calicatus
Cylicostephanus goldi
Cylicostephanus longibursatus
Cylicostephanus minutus

Petrovinema poculatum

Pinworms (adults and 4th stage larvae) - *Oxyuris equi*

Ascarids (adults and 3rd and 4th stage larvae) - *Parascaris equorum*

Hairworms (adults) - *Trichostrongylus axei*

Large-mouth stomach worms (adults) - *Habronema muscae*

Bots (oral and gastric stages) – *Gasterophilus* spp. including *G. intestinalis* and *G. nasalis*

Lungworms (adults and 4th stage larvae) - *Dictyocaulus arnfieldi*

Intestinal threadworms (adults) - *Strongyloides westeri*

Summer sores caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae; dermatitis caused by neck threadworm microfilariae, *Onchocerca* sp.

2. EFFECTIVENESS:

a. Dosage Characterization:

A dose of 200 mcg/kg of ivermectin, already established to be efficacious for nematode control for the single entity product EQVALAN® paste (NADA 134-314), was selected for the ivermectin plus praziquantel combination (EQVALAN® is a registered trademark of Merial Limited).

Based on the effectiveness of praziquantel incorporated into an ivermectin paste formulation in three non-zero levels (0.5, 1.0, and 2.0 mg/kg bodyweight) and a control, in a dose determination / confirmation study (PR&D 38501) against naturally acquired tapeworm infections in horses, a dose of 1.0 mg/kg of praziquantel was selected for treatment of tapeworms. This study is discussed in detail in the Dose Determination and Confirmation (PR&D 38501) section on page 7.

b. Substantial Evidence:

(1) Bioequivalence Study (PR&D 0046601)

Purpose: To evaluate the relative bioavailability of ivermectin when administered to horses as either the approved paste formulation (EQVALAN®) or as a combination ivermectin plus praziquantel oral paste. Both formulations are intended to deliver a target dose of 200 mcg/kg bodyweight of ivermectin.

Study Director and Study Location: Luiz Carvalho, DVM, MSc
Merial Uruguaiana Research Center
P.O. Box 150, 97500-970 Uruguaiana RS, Brazil

Animals: 30 female Crioulo horses, ranging in age from 3-8 years.

Dosage Form: Paste

Route of Administration: Oral

Dose and Frequency of Treatment: Each formulation (either ivermectin alone at a target dose of 200 mcg/kg, or ivermectin plus praziquantel paste formulation given at a target dose of 200 mcg/kg ivermectin and 1.0 mg/kg praziquantel) was administered orally once to each group of animals (based on individual bodyweight) on either Day 0 or Day 70.

Duration of Study: 122 days

Study Design The investigation was conducted as a randomized two-period, two treatment, two-sequence crossover trial with a 35-day washout interval between doses. Animals did not receive the test drug or related drugs or milbemycin three months prior to study.

The products used in this study were as follow:

- Reference Formulation: An oral paste consisting 1.87% w/w of ivermectin (EQVALAN®)
- Test Formulation: An oral paste consisting of 1.55% w/w of ivermectin and 7.75 % praziquantel

Each formulation was administered once to each of the animals. The animals were restrained for at least 6 hours prior to dosing and were allowed access to a limited quantity of hay during this period. Hay and feed were withheld from the animals for 4 hours post dosing. The horses were also observed at hourly intervals until 4 hours post dosing.

The required amount of paste was placed at the base of the tongue using a syringe. Doses were administered between 6:30 and 8:30 am. For dosing purposes, the animal weight was rounded up to the nearest 50 lbs (22.7 kg). Blood samples (~ 30 ml) were drawn at 0 (pre-dosing), 0.5, 1.0, 1.5, 3.0, 4, 6.0 7.5, 9.0, 12 and 24 hours (Day 0); subsequently, samples were drawn on Days 3, 7, 14, 21, and 35. Following a 35-day washout period, animals received the other formulation (Day 70) and sampled as with the first period. Plasma, obtained from the blood samples, was divided into multiple aliquots and stored frozen until shipped for analysis by an HPLC method using fluorescence detection.

Data Analysis: The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal method with linear interpolation from Day 0 to the last point at which drug concentration was quantified ($AUC_{0\text{-}tlast}$). AUC was also calculated for the absorption ($AUC_{0\text{-}24hr}$) and elimination ($AUC_{24hr\text{-}tlast}$) phases. C_{MAX} and T_{MAX} for each animal were taken as the observed peak and time to that observation. $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24hr}$, $AUC_{24hr\text{-}tlast}$, and C_{MAX} values were transformed to the natural logarithms and the effect of treatment on ivermectin bioavailability determined using an analysis of variance procedure (where effect terms include sequence, subject nested within sequence, period and treatment). For $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24hr}$, $AUC_{24hr\text{-}tlast}$, and C_{MAX}, upper and lower 90% confidence limits for the ratio of (ivermectin plus praziquantel)/ivermectin were calculated.

Results: The 90 percent confidence limits on the (ivermectin plus praziquantel)/ivermectin ratio for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24hr}$, and $AUC_{24hr\text{-}tlast}$ were 0.83 to 1.01, 0.73 to 1.05, and 0.85 to 1.00, respectively.

Table 1. Summary of Results (PR&D 0046601)

	Ivermectin	Ivermectin plus Praziquantel	RATIO	LCL[1]	UCL[2]
$AUC_{0\text{-}tlast}$[3]	129.73	118.63	0.91	0.83	1.01
$AUC_{0\text{-}24hr}$[3]	28.93	25.40	0.88	0.73	1.05
$AUC_{24hr\text{-}tlast}$[3]	99.70	92.06	0.92	0.85	1.00
C_{max}[4]	43.60	37.93	0.87	0.74	1.02
T_{max}[5]	8.38	8.95	-	-	-

[1] LCL = Lower Confidence Limit
[2] UCL = Upper Confidence Limit
[3] AUC = Area Under the Curve: ng-day/mL
[4] Cmax = Peak concentration: ng/mL
[5] Tmax = Time to peak concentration: hours

Conclusions: While the overall extent of ivermectin absorption is equivalent for the test (ivermectin plus praziquantel) and reference (ivermectin from EQVALAN® paste) products, the test product exhibits a slower rate of ivermectin absorption. Consequently, the ivermectin exposure during the first 24 hours postdose after exposure to the test product (as depicted by lower Cmax and AUC_{0-24} values) is less that observed with the reference formulation. This is particularly evident in the lower confidence limit values for these parameters.

To confirm that this difference will not impact the therapeutic comparability of the test and reference product, published and proprietary research information were evaluated. This type of evaluation was deemed appropriate for this application because Merial is the sponsor of the NADA for the reference formulation.

On the basis of this evaluation, CVM concludes that the slightly lower ivermectin exposure occurring during the first 24 hours after dosing will not affect product effectiveness for the existing claims on the EQVALAN® product label. Consequently, CVM concludes that the ivermectin component of the new combination oral paste will demonstrate a level of safety and effectiveness equivalent to that associated with the approved EQVALAN® product when administered at a dose of 200 mcg ivermectin/kg BW to horses.

Observations: No adverse reactions were reported.

Dose Confirmation (PR&D 0038501 and 0062302)

A dose confirmation study (PR&D 0062302) was conducted to evaluate the effectiveness of ivermectin plus praziquantel against certain cestodes and nematodes in horses, and to evaluate noninterference of the active compounds (ivermectin and praziquantel). The PR&D 0038501 study was used as both a dose determination study and as a second dose confirmation study.

(2) Dose Determination and Confirmation (PR&D 0038501)

Purpose: The objective of this study was to determine the appropriate dose level of praziquantel to be combined with ivermectin and to determine the effectiveness of praziquantel combined with ivermectin against tapeworms (*A. perfoliata*) when administered as a single oral dose to horses at the rate of 1.0 mg/kg and 200 mcg/kg, respectively, on a per bodyweight basis, in a paste formulation.

Investigator and Study Location: J. E. Holste, DVM
Merial Limited
Missouri Research Center
6498 Jade Rd.
Fulton, MO 65251 USA

Animals: 32 horses of mixed breed comprised of 9 geldings and 23 females, aged 2 to 20 years, and weighing 201 to 548 kg.

Dosage Form: Paste

Route of Administration: Oral

Dose and Frequency of Treatment: Beginning on Day 0, 8 animals/group received a single oral dose of 200 mcg/kg bodyweight ivermectin and either 0.5, 1.0, or 2.0 mg/kg bodyweight praziquantel.

Controls: Control horses were sham-dosed with empty syringes in the same manner as those treated with the test article.

Duration of Study: 6 days

Study Design: Animals were allocated on Day –3 by randomization based on pre-treatment fecal cestode counts and bodyweight into either a control group or groups that received ivermectin plus praziquantel. Worm burdens were determined at necropsy by replicate on Days 5 and 6.

Data Analysis: Counts of each parasite species for each animal were calculated by multiplying the number of worms counted in each location by the aliquot factor and summing over locations. All counts were transformed to the natural logarithm of (count + 1) for analysis and calculation of geometric means. Percent effectiveness was calculated using the following formula: 100 X (1-TRMT/CNTL). Treatment comparisons were made using Wilcoxon's rank sum statistic.

Results: The study showed that the groups treated with ivermectin/praziquantel at either 0.5, 1.0 or 2.0 mg/kg had significantly ($p<0.01$) fewer adult *Anoplocephala perfoliata* than the control group. The study also showed that the groups treated with ivermectin/praziquantel at either 1.0 or 2.0 mg/kg had significantly ($p<0.05$) fewer adult *Anoplocephala perfoliata* than the group with 0.5 mg/kg. The difference in adult *A. perfoliata* counts for groups treated with ivermectin/praziquantel at 1.0 and 2.0 mg/kg were not significant ($p=1.00$). The effectiveness of the 0.5 mg/kg group was 92%. The effectiveness of the 1.0 mg/kg group and the 2.0 mg/kg group was >99% and 100% respectively. Thus a dose of 1.0 mg/kg of praziquantel was selected for treatment of tapeworms.

Table 2. Summary of *Anoplocephala perfoliata* (adult) Geometric Mean Data at 0, 0.5, 1.0, and 2.0 mg/kg Bodyweight Praziquantel (PR&D 0038501)

	Control[b]	Ivermectin/ Praziquantel 0.5 mg/kg	Ivermectin/ Praziquantel 1.0 mg/kg	Ivermectin/ Praziquantel 2.0 mg/kg
Geometric mean[a]	33.8	2.7	0.1	0.0
Effectiveness	N/A	92%	>99%	100%

[a]Geometric mean, based on transformation to ln (count + 1); eight animals per treatment.
[b]At least 6 adequately infected control animals

The ivermectin plus praziquantel paste was readily accepted by all treated animals.

Conclusions: Ivermectin plus praziquantel oral paste for horses, administered at 200 mcg/kg bodyweight ivermectin plus 1.0 mg/kg bodyweight praziquantel, demonstrated effectiveness against natural infections of *A. perfoliata*.

Observations: No adverse reactions were reported.

(3) Dose Confirmation and Noninterference (PR&D 0062302)

Purpose: The objective of this study was to confirm the effectiveness and noninterference of praziquantel combined with ivermectin against cestodes (*A. perfoliata*) and nematodes when administered in a paste formulation as a single oral dose to horses at the target dose of 1.0 mg/kg and 200 mcg/kg, respectively.

Investigator and Study Location: Craig Reinemeyer, DVM, PhD
Forkadeer Farm,
Ninemile Crossroad
P.O. Box 145-F, Pikeville, TN 37367, USA

Animals: 32 horses of mixed breed comprising 6 males, 13 male-castrates, and 13 females, aged 1 to 20 years, and weighing 236 to 555 kg.

Dose Form: Paste

Route of Administration: Oral

Dose and Frequency Of Treatment: All treatments were administered orally once on Day 0 and included the following oral paste formulations and target doses: ivermectin at 200 mcg/kg plus praziquantel at 1.0 mg/kg bodyweight, ivermectin at 200 mcg/kg bodyweight or praziquantel at 1.0 mg/kg bodyweight.

Controls: Control horses were sham-dosed with empty syringes in the same manner as those treated with the test article.

Duration of Study: 14-15 days

Study Design: The study, which utilized naturally infected horses, was conducted in three phases. Acceptability of the paste was assessed immediately after administration to each animal receiving the ivermectin plus praziquantel treatment. Worm burdens were determined at necropsy by replicate on Days 14 and 15.

Data analysis: Calculation of geometric means for parasite species was performed. Pairwise treatment comparisons comparing the ivermectin plus praziquantel group to the control and the ivermectin group to the ivermectin plus praziquantel group were made using Wilcoxon's rank sum statistic.

Results: To prove non-interference, effectiveness data was compared among the four treatment groups for *Anoplocephala perfoliata* and at least four representative species in four different small strongyle genera. There were no differences in effectiveness against *A. perfoliata* when comparing the ivermectin plus praziquantel to praziquantel alone ($p>0.25$); nor were differences detected in effectiveness against strongyles when comparing the ivermectin plus praziquantel to ivermectin alone ($p>0.25$). See Tables 3, 4, and 5.

Table 3. Geometric Means (worms / horse)

Parasite	Control	Combination	Ivermectin	Praziquantel
Anoplocephala perfoliata	13.5	0.1	23.9	0.7
Coronocyclus coronatus	34.6	0.0	0.0	38.5
Cyathostomum catinatum	3028.6	2.1	1.8	20978.1
Cylicocyclus leptostomum	278.0	0.8	5.2	1131.2
Cylicostephanus longibursatus	744.0	0.5	1.3	21068.2

Table 4. Probability values from Wilcoxon's rank sum test comparing each treatment group to the Ivermectin/Praziquantel Combination

Parasite	Control vs. Combination	Ivermectin vs. Combination	Praziquantel vs. Combination
Anoplocephala perfoliata	<0.01	<0.01	>0.25
Coronocyclus coronatus	<0.01	>0.25	<0.05
Cyathostomum catinatum	<0.01	>0.25	<0.01
Cylicocyclus leptostomum	<0.01	>0.25	<0.01
Cylicostephanus longibursatus	<0.01	>0.25	<0.01

Table 5. Percent effectiveness compared to the Control, using geometric means

Parasite	Combination vs. Control	Ivermectin vs. Control	Praziquantel vs. Control
Anoplocephala perfoliata	>99%	0.0%	94.6%
Coronocyclus coronatus	100%	100%	0.0%
Cyathostomum catinatum	>99%	>99%	0.0%
Cylicocyclus leptostomum	>99%	98.1	0.0%
Cylicostephanus longibursatus	>99%	>99%	0.0%

For purposes of dose confirmation, effectiveness data for *Anoplocephala perfoliata* was examined. Compared to controls, counts for adult *A. perfoliata* were significantly ($p<0.01$) lower for horses treated with ivermectin plus praziquantel with an effectiveness of >99%.

Table 6. Summary of *Anoplocephala perfoliata* (adult) Geometric Mean Data at 1.0 mg/kg Bodyweight Praziquantel (PR&D 0062302)

	Control[b]	Ivermectin/Praziquantel 1.0 mg/kg
Geometric mean[a]	13.5	0.1
Effectiveness	N/A	>99%

p<0.01; Probability values from Wilcoxon's rank sum test

[a]Geometric mean, based on transformation to ln (count + 1); eight animals per treatment.

[b]At least 6 adequately infected control animals.

Conclusions: Ivermectin plus praziquantel oral paste for horses, administered at 200 mcg/kg bodyweight ivermectin plus 1.0 mg/kg bodyweight praziquantel, demonstrated effectiveness against natural infections of *Anoplocephala perfoliata* and nematodes. No interference in the effectiveness or safety of the individual components, ivermectin and praziquantel, was evident when ivermectin and praziquantel were combined in an oral paste.

Observations: No adverse reactions were reported.

(4) Field Studies (PR&D 0047001 – 0047006)

Six well-controlled, masked, field studies were conducted under the same protocol. The studies were conducted in a wide variety of geographical locations including five in the US and the sixth one conducted in Canada.

Purpose: The objective of these studies was to confirm the effectiveness and safety of praziquantel combined with ivermectin against cestodes and nematodes when administered as a single oral dose to horses under field use conditions.

Investigators and Study Locations:

Study	Investigator	Location
PR&D 0047001	C. Reinemeyer, PhD, DVM	Strawberry Plains, TN 37871 USA
PR&D 0047002	M. Doucet, DVM	Quebec, Canada
PR&D 0047003	J. E. Holste, DVM	Fulton, MO 65251 USA
PR&D 0047004	A. Paul, DVM, MS	Urbana, IL 61801 USA
PR&D 0047005	L. L. Smith, DVM	Lodi, WI 53555 USA
PR&D 0047006	C. Fenger, DVM, PhD	Nicholasville, KY 40356 USA

Animals: A total of 149 horses, representing a variety of breeds, 83 females, 14 males, and 52 male castrates, weighing 139 to ~964 kg, and aged 3 months to 25 years, were utilized in the six field studies. Of the 149 horses in the studies, all were nematode positive and 83 were cestode positive at the beginning of the studies.

Table 7. Combined Field Studies (PR&D 0047001 – 0047006)

Trt. Group	Drug	Dose	Total No. Animals	Nematode Positive	Cestode Positive
1	Empty Syringe	N/A	37	37	21
2	Ivermectin plus Praziquantel	200 mcg/kg Ivermectin + 1.0 mg/kg Praziquantel	112	112	62
			149	149	83

Dosage Form: Paste

Route of Administration: Oral

Dose and Frequency of Treatment: Ivermectin plus praziquantel oral paste was administered once on Day 0 to provide a target dose of 200 mcg/kg bodyweight of ivermectin and 1.0 mg/kg bodyweight of praziquantel.

Controls: Control horses were untreated.

Duration of Study: 17 days

Study Design: Fecal samples were collected at various times prior to treatment between Day -28 and Day 0. Following treatment on Day 0, fecal samples were generally collected on Days 7, 8, 9, 14, 15, and 16.

Data Analysis: Fecal egg counts for nematodes, for each animal and each time point, were transformed to the natural logarithm of (count + 1) for calculation of geometric means (GM). Percent effectiveness was calculated using the following formula: 100 X (1-TRMT/CNTL). Treatment comparisons were made for nematode eggs using Wilcoxon's rank sum statistic with a significance level of 0.05.

For assessing effectiveness against tapeworms, animals with at least one positive cestode count before treatment were considered positive. Likewise, any animal with at least one positive cestode count after treatment was also considered positive.

Results: For each of the six studies, horses treated with ivermectin plus praziquantel as a paste formulation had significantly ($p<0.01$) fewer nematode (strongyle) eggs than the controls at each post-treatment time point.

To evaluate effectiveness against tapeworms, a total of 83 cestode positive horses (62 treated and 21 controls) were included in a cross-study analysis. The following table is a compilation of this data:

Table 8. Change in Cestode Infection Status for Horses Detected Cestode Positive Pre-treatment

Treatment	No. of Horses	Post-Treatment Cestode Status	
		Negative	Positive
Untreated Control	21	0 (0%)	21 (100%)
Combination Drug	62	58 (94%)	4 (6%)

Fisher's exact test, $p<0.0001$

Observations: No adverse reactions were reported, and the paste was readily accepted by treated animals.

Conclusions: The ivermectin plus praziquantel oral paste formulation administered to horses at 200 mcg/kg ivermectin bodyweight and 1.0 mg/kg praziquantel bodyweight is safe, acceptable and effective for the treatment of nematode and cestode infections under North American field conditions.

3. TARGET ANIMAL SAFETY:

a. Oral Safety Study in Foals (PR&D 0062601)

Purpose: To determine the safety profile of a combination of ivermectin plus praziquantel when administered in an oral paste formulation to horses at 1, 3, or 5X the target use level three times at two-week intervals.

Investigator and Study Location: John Holste, DVM
Merial Limited
Missouri Research Center
6498 Jade Road
Fulton, MO 65251 USA

Animals: 24 foals (12 males, 12 females), ranging in age from 5 to 6 months.

Dosage Form: Paste

Route of Administration: Oral

Dose and Frequency of Treatment: Foals were dosed at two-week intervals, for a total of three administrations, at approximately 200 mcg/kg ivermectin plus 1.0 mg/kg praziquantel, 600 mcg/kg ivermectin plus 3 mg/kg praziquantel, or 1000 mcg/kg ivermectin plus 5 mg/kg praziquantel (1, 3, or 5X, respectively). There were 6 foals (3 males, 3 females) per group. Animals were dosed based on bodyweight.

Controls: 6 control foals (3 males, 3 females) were sham-dosed with empty syringes in the same manner as those treated with the test article.

Duration of Study: 36-37 days

Evaluation: Foals were observed prior to treatment, at 1, 2, 3, 4, 8, 12, and 24 hours after treatment and twice daily on non-treatment days. Blood samples were collected for evaluation of blood chemistry and hematology 7 days prior to treatment and on Days 0, 7, 14, 21, 28, and 35. Full necropsy and tissue collection was performed after euthanasia on Day 35 or 36 on all horses. Histopathological exams were performed on harvested tissues from the six control horses and the six 5X horses only.

Results: No treatment-related effects were observed. In the blood chemistry and hematology evaluations, no significant trends were established either in dose response between groups or over time within groups. Moreover, all variables generally fell within reference ranges with the notable exception being a mild leukocytosis and eosinophilia that was present in all four groups during most of the study. The leukocytosis was probably due to early weaning and exposure to strangles, and the eosinophilia was probably due to internal parasitism. The same two trends were noted in the histopathologic data: (a) all 12 horses showed signs consistent with strangles (inflammation and hyperplasia of lungs and lymph nodes) and (b) all 12 horses showed signs of recent intestinal parasitism (inflammation with large numbers of eosinophils in the digestive tract).

Conclusion: Ivermectin plus praziquantel is safe when administered to foals at 200 mcg/kg ivermectin plus 1.0 mg/kg praziquantel (1X), 600 mcg/kg ivermectin plus 3.0 mg/kg praziquantel (3X), or 1000 mcg/kg ivermectin plus 5.0 mg/kg praziquantel (5X) on three consecutive occasions, at two-week intervals.

b. 10X Tolerance Study in Adult Horses (PR&D 0050701)

Purpose: To evaluate the safety of ivermectin plus praziquantel when administered orally once to adult horses at approximately 2000 mcg/kg bodyweight plus 10.0 mg/kg bodyweight praziquantel (10X the use level).

Study Director and Study Location: Luiz Carvalho, DVM
Merial Uruguaiana Research Center
P.O. Box 150
97500-970 Uruguaiana RS, Brazil

Animals: 6 adult Crioulo horses (3 males, 3 females), ranging in age from 3.5 to 4.5 years.

Dosage Form: Paste

Route of Administration: Oral

Dosage and Frequency of Treatment: Horses were dosed once with ivermectin plus praziquantel at 2000 mcg/kg ivermectin plus 10.0 mg/kg praziquantel (10X). Two males and two females received this dosage.

Controls: 2 control horses (1 male, 1 female) were sham-dosed using empty syringes.

Duration of Study: 15 days

Evaluation: Physical examinations were conducted on Day -4, immediately after treatment, and on Days 7 and 14, and blood samples were collected for evaluation of blood chemistry and hematology on Day -1, about 12 hours after treatment, and on Days 7 and 14.

Results: No treatment-related effects were observed. Only minor fluctuations were noted in any of the blood chemistry or hematology parameters, and none of the values were outside normal reference range. No dose related effect was observed. No statistical analysis was performed due to the small sampling size of the study. No horses died during the study so no necropsies were performed.

Conclusion: Ivermectin plus praziquantel is safe when administered once to adult horses at approximately 2000 mcg/kg bodyweight ivermectin plus 10.0 mg/kg bodyweight praziquantel (10X).

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

The label states the following: “Not for use in humans. Keep this and all drugs out of reach of children.” “Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes.”

5. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 514 of the implementing regulations.
The data demonstrates that Zimecterin® Gold Paste, when used under labeled conditions, is safe and effective.

Zimecterin® Gold Paste is labeled for OTC use. Routine deworming of horses is a widely accepted and recommended practice performed by the lay person. A diagnosis of parasite infection prior to deworming is not necessary.

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.

A U.S. patent for Zimecterin Gold is pending.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Package Outsert

Syringe Label

Syringe Carton