HFA-305

Approval Date APR 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


NADA 141-214 FOIS

## TABLE OF CONTENTS


| | Page |
|---|---|
| 1. General Information | 3 |
| 2. Effectiveness | 5 |
| a. Dosage Characterization | 5 |
| b. Substantial Evidence | 5 |
| 3. Target Animal Safety | 13 |
| 4. Human Safety | 15 |
| 5. Agency Conclusions | 15 |
| 6. Attachments | 15 |

# Freedom of Information Summary

## 1. GENERAL INFORMATION:

| | |
|---|---|
| a. NADA Number: | NADA 141-214 |
| b. Sponsor: | Merial Limited<br>Bldg. 500<br>3239 Satellite Blvd.<br>Duluth, GA 30096-4640 USA<br><br>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

Component Number

# ZIMECTERIN GOLD

ivermectin 1.55 % / praziquantel 7.75 % Paste

NADA 141-261, Approved by FDA

**Net Wt 0.26 oz (7.35 g)**

FPO

3 50604-30582 8

**INDICATIONS:** Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism. ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste provides effective treatment and control of the following parasites in horses. **Tapeworms** - *Anoplocephala perfoliata*, **Large Strongyles** (adults) - *Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equinus*, *Triodontophorus* spp. including *T. brevicauda* and *T. serratus* and *Craterostomum acuticaudatum*; **Small Strongyles** including those resistant to some benzimidazole class compounds (adults and fourth-stage larvae) – *Coronocyclus* spp. including *C. coronatus*, *C. labiatus* and *C. labratus*, *Cyathostomum* spp. including *C. catinatum* and *C. poteratum*, *Cylicocyclus* spp. including *C. insigne*, *C. leptostomum*, *C. nassatus*, and *C. brevicapsulatus*, *Cylicodontophorus* spp., *Cylicostephanus* spp., including *C. calicatus*, *C. goldi*, *C. longibursatus* and *C. minutus*, and *Petrovinema poculatum*; **Pinworms** (adults and

1

fourth-stage larvae) - *Oxyuris equi*; **Ascarids** (adults and third- and fourth-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 fourth-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.

**DOSAGE AND ADMINISTRATION:** This syringe contains sufficient paste to treat one 1250 lb horse at the recommended dose rate of 91 mcg ivermectin per lb (200 mcg/kg) body weight and 454 mcg praziquantel per lb (1 mg/kg) body weight. Each weight marking on the syringe plunger delivers enough paste to treat 250 lb body weight.

2

(1) While holding plunger, turn the knurled ring on the plunger 1/4 turn to the left and slide it so the side nearest the barrel is at the prescribed weight marking. (2) Lock the ring in place by making a 1/4 turn to the right. (3) Make sure that the horse's mouth contains no feed. (4) Remove the cover from the tip of the syringe. (5) Insert the syringe tip into the horse's mouth at the space between the teeth. (6) Depress the plunger as far as it will go, depositing paste on the back of the tongue. (7) Immediately raise the horse's head for a few seconds after dosing.

**PARASITE CONTROL PROGRAM:** All horses should be included in a regular parasite control program with particular attention being paid to mares, foals and yearlings. Foals should be treated initially at 5 months of age, and routine treatment repeated as frequently as every 8 weeks. Consult your veterinarian for a control program to meet your specific needs.

3

ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste controls gastrointestinal cestodes, nematodes and bots of horses. Regular treatment will reduce the chances of verminous arteritis caused by *Strongylus vulgaris*.

**PRODUCT ADVANTAGES: Broad-spectrum Control** – ZIMECTERIN® GOLD Paste kills important internal parasites, including tapeworms, bots and the arterial stages of *S. vulgaris*, with a single dose. ZIMECTERIN® GOLD Paste is a potent antiparasitic agent that is neither a benzimidazole nor an organophosphate.

**ANIMAL SAFETY:** ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste may be used in horses five months of age or older. ZIMECTERIN® GOLD has not been tested in foals younger than five months of age, in pregnant mares or breeding stallions. ZIMECTERIN® GOLD, when tested at 1, 3 and 5-times the maximum recommended dose every two weeks in 5-month old foals, and at 10-times the maximum recommended dose in a separate study, did not elicit any adverse clinical signs of toxicity.

**WARNING: Do not use in horses intended for food purposes. Not for use in humans. Keep this and all drugs out of reach of**

4

**children.** Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

**PRECAUTIONS:** ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste has been formulated specifically for use in horses **only**. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

**Environmental Safety:** Ivermectin and excreted ivermectin residues may adversely affect aquatic organisms. Do not contaminate ground or surface water. Dispose of the syringe in an approved landfill or by incineration.

**INFORMATION FOR HORSE OWNERS:** Swelling and itching reactions after treatment with ivermectin have occurred in horses carrying heavy infections of neck threadworm (*Onchocerca* sp microfilariae). These reactions were most likely the result of microfilariae dying in large numbers. Symptomatic treatment may be advisable. Consult your veterinarian should any such reactions occur. Healing of summer sores involving extensive tissue changes may require other appropriate therapy in conjunction with

5

treatment with ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste. Reinfection, and measures for its prevention, should also be considered. Consult your veterinarian if the condition does not improve.

**STORAGE:** Store up to 86°F (30°C). Transient exposure to temperatures up to 104°F (40°C) is permitted.

Merial Limited, a company limited by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex CM19 5TG, England, and domesticated in Delaware, USA as Merial LLC.

U.S. Pat. Pending

ZIMECTERIN® is a registered trademark of Merial.

Copyright© 2002 Merial Limited.
All Rights Reserved.

October 2002

6

Unvarnished & unprinted
area at top for overlap
3-15/16"W x 1/4" H

60011

# ZIMECTERIN®

GOLD

Ivermectin 1.50 praziquantel 7.75 g

For Treatment and Control of Tapeworms, Large Strongyles, Small Strongyles, Pinworms, Roundworms (Ascarids), Hairworms, Neck Threadworms, Large-mouth Stomach Worms, Bots. See carton for complete indications and use directions. Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

NADA 141-214, Approved by FDA

**Net Wt. 0.26 oz (7.35 g)** 1021-0518-00

**WARNING: Do not use in horses intended for food purposes.**

**Not for use in humans. Keep this and all drugs out of reach of children.** Refrain from smoking or eating when handling. Wash hands after use. Avoid contact with eyes.

**STORAGE:** Store up to 86°F (30°C). Transient exposure to temperatures up to 104°F (40°C) is permitted.

Lot No & Exp Date

ZIMECTERIN® is a registered trademark of Merial.
Copyright © 2002 Merial Limited. All Rights Reserved.

Marketed by Merial Limited, Duluth, GA 30096-4640

U.S. Pat. Pending October 2002

MERIAL

Unvarnished & unprinted area
(Magenta outlined area does not print)
1-5/16"W x 5/16' H

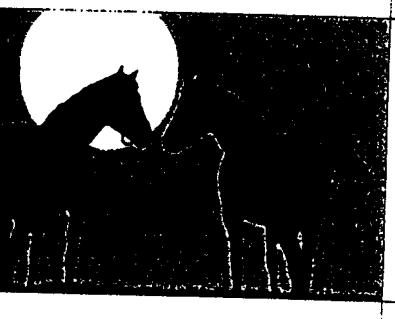
Merial Component number

# ZIMECTERIN® GOLD

(ivermectin 1.55% / praziquantel 7.75%) Paste

REMOVES ROUNDWORMS, TAPEWORMS AND BOTS WITH A SINGLE DOSE. FOR ORAL USE IN HORSES ONLY

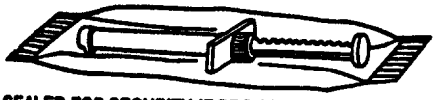
NADA 141-214, Approved by FDA



MERIAL

CONTENTS WILL TREAT UP TO 1250 lb BODY WEIGHT. Net Wt. 0.26 oz (7.35g)

ZIMECTERIN® GOLD



SEALED FOR SECURITY. IF BROKEN, DO NOT ACCEPT.

Product No. 60011 U.S. Pat. Pending

ZIMECTERIN® is a registered trademark of Merial.

Copyright © 2002 Merial Limited.
All Rights Reserved.

ZIMECTERIN® GOLD
(ivermectin 1.55% / praziquantel 7.75%) Paste

ZIMECTERIN® GOLD

WARNING: Do not use in horses intended for food purposes.

Keep this and all drugs out of reach of children.

Safety Data Sheet (MSDS) containing more detailed information regarding safety information, to report adverse reactions or injury, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

PRECAUTIONS: ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste has been formulated specifically for use in horses only. This product should not be used in other animal species or severe adverse reactions, including fatalities, may occur.

Ivermectin-sensitive dogs exposed to ivermectin products may develop a drug related neurologic response characterized by ataxia, coma, tremors, mydriasis, depression, and recumbency followed by death in the absence of supportive care. Do not administer ZIMECTERIN® GOLD Paste orally or topically to dogs or other non-target animals. Keep out of the reach of children and pets. Do not contaminate ponds, waterways, or wetlands with chemicals or empty containers.

STORAGE: Store up to 86°F (30°C). Accidental exposure to temperatures up to 104°F (40°C) is permitted.

INDICATIONS: Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasites. ZIMECTERIN® GOLD (ivermectin/praziquantel) Paste provides effective treatment and control of the following parasites in horses.

Roundworms – Parascaris equorum (Ascaris), Large Strongyles (adults), Strongyles species (adults only), Strongyles – Anoplocephala perfoliata, Large Strongyles (adults), Small Strongyles including Cyathostomes and Cylicostomes, Bots – Gasterophilus species including G. intestinalis (late larval stages), G. nasalis, G. nigricornis, G. pecorum, Bots – Dermatobia species including D. hominis and Cuterebra species including C. leconi and C. lepivora, Oxyuroidea species including Oxyuris equi, Pinworms – Oxyuris species including C. equi and C. equina, Oxyuroidea species including C. leconi and C. lepivora, Oxyuroidea species including C. equi, Oxyuroidea species including C. equi