Date of Approval: May 12, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-421

DUOCARE

Ivermectin 1.87% / praziquantel 23.38% Paste

Horses

For the treatment and control of gastrointestinal nematodes, cestodes, and bots in horses over 5 months of age

Sponsored by:

Merial Limited

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I. GENERAL INFORMATION

A. File Number

NADA 141-421

B. Sponsor

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

Drug Labeler Code: 050604

C. Proprietary Name

DUOCARE

D. Established Name

Ivermectin 1.87% / praziquantel 23.38%

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Paste

G. Amount of Active Ingredient

Each milligram of DUOCARE paste contains 0.0187 mg (1.87%) ivermectin and 0.2338 mg (23.38%) praziquantel. Each syringe contains 113.75 mg of ivermectin and 1421.5 mg of praziquantel.

H. 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 bodyweight.

I. Dispensing Status

OTC

J. Dosage Regimen

200 mcg ivermectin and 2.5 mg praziquantel per kilogram bodyweight

K. Route of Administration

Oral

L. Species/Class

Horse

M. Indication

For the treatment and control of the following parasites in horses over 5 months of age:

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 (adults, including those resistant to some benzimidazole class compounds)
Coronocyclus spp. including *C. coronatus*, *C. labiatus* and *C. labratus*,
Cyathostomum spp. including *C. catinatum* and *C. pateratum*
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

Small Strongyles
Fourth-stage larvae

Pinworms (adults and 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.

II. EFFECTIVENESS

A. Dosage Characterization

Ivermectin

The dose of ivermectin (200 mcg/kg; 0.2 mg/kg) was selected based on the approved dose in NADA 134-314 for ivermectin paste 1.87%, and a study in naturally infected ponies.

In one study, 16 naturally infected Dartmoor ponies, less than 1 year of age, were randomized to one of two groups: treatment with 0.2 mg/kg ivermectin and 2.5 mg/kg praziquantel (n=8), or no treatment (n=8). The ponies were euthanized and necropsied at either 14 (ponies administered no treatment) or 15 (ivermectin/praziquantel treated ponies) days following treatment. In ivermectin/praziquantel treated animals, the ivermectin/praziquantel product was 99.9% effective against bots, 100% against ascarids, 100% against large strongyles, and 99.96% against immature and adult cyathostomes. No adverse reactions to the drug product were encountered during the study.

Praziquantel

The dose of praziquantel (2.5 mg/kg) was selected based on published literature suggesting the effectiveness of this dose, and the use of ivermectin/praziquantel combination products in horses in other countries. In a paper by Lyons[1], a 1.0 mg/kg dose of praziquantel removed 89-100% (n=6) of *A. perfoliata* when administered by stomach tube, and 100% (n=2) when administered orally. No adverse events were seen in any of the treated horses. In a paper by Parker and Bairden, a moxidectin/praziquantel combination product (praziquantel dosed at 2.5 mg/kg) administered orally to horses removed 100% (n=12) of *A. perfoliata* when compared to control group (n=12)[2]. In one study, 12 horses were treated with a combination ivermectin/praziquantel formulation, dosed at 2.5 mg/kg praziquantel. On necropsy 24 hours later, 6 horses had *A. perfoliata*. All worms were considered dead based on location in the gastrointestinal tract, suggesting removal of all live *A. perfoliata*. In another study, 16 naturally infected Dartmoor ponies, less than 1 year of age, were randomized to one of two groups: treatment with 0.2 mg/kg ivermectin and 2.5 mg/kg praziquantel (n=8), or no treatment (n=8). The ponies were euthanized and necropsied at either 14 (ponies administered no treatment) or 15 (ivermectin/praziquantel treated ponies) days following treatment. Animals administered no treatment had a mean of 3.4 *A. perfoliata* worms per animal while ivermectin/praziquantel treated animals had no *A. perfoliata*. No adverse reactions were reported in any of these studies when horses were dosed at 2.5 mg/kg praziquantel. Due to consistent removal of *A. perfoliata* seen in these preliminary studies, the praziquantel dose of 2.5 mg/kg was chosen to be tested in pivotal studies.

B. Substantial Evidence

1. Dose Confirmation

a. Title: Dose Confirmation Study of Praziquantel Oral Paste for the Elimination of Intestinal Cestode Infections in Horses (Study #144-5-775-1001, November 2004)
b. Investigator: Craig Reinemeyer, DVM, PhD
Knoxville, TN
c. Study Design:
(1) Objective: To confirm the effectiveness of 2.5 mg/kg praziquantel oral paste for the treatment of tapeworm (*A. perfoliata*) infections in horses.

[1] Lyons, E.T. et al. 1992. "Activity of Praziquantel Against Anoplocephala perfoliata (Cestoda) in Horses" *J. Helminthol. Soc. Washington* 59(1): 1-4.
[2] Parker, L.D., Bairden, K. 2001. "Evaluation of Efficacy of a Combination Moxidectin/Praziquantel Oral Gel Formulation Against Bots and Tapeworms in Horses". Moxidectin Symposium, 18th WAAVP Conference, Stressa, Italy; Fort Dodge CD-ROM of Proceedings.

(2) Study Animals: 16 adult horses (9 males, 7 females) of various breeds ranging from 1.5 to 22 years of age were enrolled and randomly assigned to one of two treatment groups. Presence of cestode eggs in fecal samples was confirmed within 30 days of treatment for all horses.

(3) Treatment Groups: Animals (n=8) in the test group received praziquantel 2.5 mg/kg in an oral paste formulation similar to the final formulation, without the ivermectin component. The control group was administered the vehicle paste (n=8) in an equal volume.

(4) Drug Administration: Assigned treatment was administered orally, once.

(5) Study Variables: The primary variable was the total number of *A. perfoliata* collected from the gastrointestinal tract of each horse upon necropsy on Day 9 or 10 following treatment. Physical examinations and twice daily clinical observations were conducted to assess health and monitor for adverse reactions. Personnel making clinical and parasitological assessments were masked to treatment assignment.

(6) Statistical Methods: Geometric mean parasite counts were evaluated using the Mann-Whitney (non-parametric) test to detect significant differences between treated and control animals.

d. Results: All eight vehicle control horses had parasite burdens in excess of 10 individual *A. perfoliata* (range 25 to 251), confirming adequacy of tapeworm infection in the study. Geometric mean tapeworm counts for the vehicle controls (110.05) and praziquantel treated horses (0.0) were significantly different ($P<0.05$). Effectiveness of praziquantel paste was calculated as 100%.

e. Adverse Reactions: No treatment related adverse events occurred during the study period.

f. Conclusion: Praziquantel paste for horses administered at a dose of 2.5 mg/kg demonstrated effectiveness against natural infections of *A. perfoliata*.

2. Dose Confirmation and Non-Interference

a. Title: Non-Interference and Dose Confirmation Study of Ivermectin and Praziquantel Oral Paste in the Treatment of Cyathostome and Cestode (*A. perfoliata*) Infections in Horses. (Study #254-5-802-605, Sept. 2008-May 2010)

b. Investigators:
Craig R. Reinemeyer, DVM, PhD
Rockwood, TN

Morgan McArthur, DVM
Readstown, WI

c. Study Design:

(1) Objective: To demonstrate that combining the two active ingredients (ivermectin and praziquantel) does not impact the effectiveness of each active as used individually (non-interference), to confirm the effectiveness of 2.5 mg/kg of praziquantel for the treatment of *A. perfoliata* infections, and to

confirm the effectiveness of ivermectin for the treatment of any of the cyathostome species that constituted adequate infection in the study population.

(2) Study Animals: In cohorts of 4 or 8 horses each, at two geographically distinct sites, 32 adult horses (9 males, 23 females) of various breeds, ranging from 1.5 to 18 years of age, were randomized to one of four treatment groups, 8 horses per group. Presence of cestode and strongyle eggs in feces was confirmed within 30 days of treatment for all horses.

(3) Treatment groups: Treatment groups are summarized in Table 1.

Table 1: Treatment Groups

Treatment Group	Treatment	Dose mg/kg	Number of Animals
1	Control- Tap water	Approximately 5 mL/horse	8
2	Ivermectin paste	200 mcg/kg	8
3	Praziquantel paste	2.5 mg/kg	8
4	Ivermectin/praziquantel paste (DUOCARE)	200 mcg/kg ivermectin; 2.5 mg/kg praziquantel	8

(4) Drug Administration: Treatment was administered orally as a single dose.

(5) Study Variables: Twice daily clinical observations, observations immediately following treatment, pre- and post-treatment physical examinations, and pre- and post-treatment body weight were recorded. On Day 8 or 9 post-treatment, horses were euthanized and necropsy performed. The gastrointestinal tract and its contents were collected from each horse and examined for the presence of parasites. Parasites were identified to genus and species, and counted. Personnel conducting clinical and parasitological assessments were masked to treatment assignment.

(6) Statistical Methods: Geometric mean worm counts for species with adequate infection were compared to the control using a one-way ANOVA and if the effect of treatment was statistically significant ($P<0.05$), between-treatment comparisons were made. The combination group was compared to ivermectin or praziquantel treated group to justify the need for the combination and assess non-interference. If these contrasts were statistically significant, the percent efficacy was calculated. To confirm the effectiveness of praziquantel against tapeworms and ivermectin against cyathostomes, the praziquantel/ivermectin treated group was compared to the control via the method described above. If this contrast was significant, the percent efficacy was calculated.

d. Results: Adequacy of infection criteria were met for *A. perfoliata*, 9 adult cyathostome species, and undifferentiated L4. Effectiveness was calculated by comparing the geometric mean number of worms in the control group with that of the treated groups. See Table 2 for the geometric mean worm count for each parasite for each treatment group. See Table 3 for calculated percent effectiveness. Statistically significant differences were also seen when comparing treatment groups with the control. When praziquantel or ivermectin/praziquantel treatments were compared to control for *A. perfoliata*, differences were statistically significant with P=0.0005. When ivermectin or ivermectin praziquantel treatments were compared to control for each cyathostome species, differences were statistically significant with all P values <0.05.

Table 2: Geometric Means of Worm Counts for Each Treatment Group

Parasite	# of Infected Controls	Control (Mean # of Worms)	Ivermectin (Mean # of Worms)	Praziquantel (Mean # of Worms)	Ivermectin Praziquantel (Mean # of Worms)
Anoplocephala perfoliata	6	13.73	5.88	0	0
Cylicocyclus nassatus	8	6958.92	0	1592.29	0
Cylicocyclus leptostomum	7	949.53	0	377.75	0
Cylicocyclus insigne	6	105.65	0	101.18	0
Cyathostomum catinatum	8	8141.59	0	4921.39	0.78
Coronocyclus coronatus	6	71.97	0.78	91.59	0
Cylicostephanus longibursatus	8	8890.55	0	14919.41	0
Cylicostephanus goldi	8	2818.25	0	1618.11	0
Cylicostephanus calicatus	6	397.06	0	1500.48	0
Cylicostephanus minutus	7	1811.7	0	802.47	0
Undifferentiated L4	8	18518	816	12623	65

Table 3: Calculated Effectiveness When Compared to Control Group

Parasite	Ivermectin	Praziquantel	Ivermectin/Praziquantel
Anoplocephala perfoliata	57.2%	100%	100%
Cylicocyclus nassatus	100%	77.1%	100%
Cylicocyclus leptostomum	100%	60.2%	100%
Cylicocyclus insigne	100%	4.2%	100%
Cyathostomum catinatum	100%	39.6%	99.99%
Coronocyclus coronatus	98.9%	0%*	100%
Cylicostephanus longibursatus	100%	0%*	100%
Cylicostephanus goldi	100%	42.6%	100%
Cylicostephanus calicatus	100%	0%*	100%
Cylicostephanus minutus	100%	55.7%	100%
Undifferentiated L4	95.6%	33.8%	99.6%

*These are not actual calculated numbers, as the mean worm count was higher in the praziquantel treated group, making the calculated % effectiveness a negative number

e. Adverse Reactions: 3 horses had transient soft feces at some point following treatment. 2 were treated with praziquantel only and 1 was treated with the ivermectin/praziquantel combination product.

On average, horses enrolled in Groups 3 and 4 (praziquantel treated groups) lost more weight than controls or those treated with Ivermectin Paste. Mean weight loss in Groups 3 and 4 was about 2%.

f. Conclusion: DUOCARE demonstrated the effectiveness of 2.5 mg/kg praziquantel against naturally occurring infections of *A. perfoliata*, and effectiveness of 200 mcg/kg ivermectin against naturally occurring infections of 9 different adult cyathostome species and undifferentiated L4. The study also demonstrates that the presence of either active ingredient in the combination does not interfere with the effectiveness of the other active ingredient (non-interference). The presence of both ingredients is more effective against a broader spectrum of parasites than either one alone.

3. Field effectiveness

a. Title: Multi-center Field Study of Ivermectin and Praziquantel Oral Paste for the Treatment of Cestode and Nematode Infections in Horses (Study #149-5-775-1001, Nov. 2005-Oct. 2008)
b. Investigators:
Craig R. Reinemeyer, DVM, PhD
Rockwood, TN

John J. Dascanio, VMD
Blacksburg, VA

Gary W. White, DVM
Sallisaw, OK

Allan J. Paul, DVM
Urbana, Illinois

c. Study Design:

(1) Objective: To confirm the effectiveness and safety of DUOCARE in horses under the proposed conditions of use. Effectiveness was approximated using presence/absence of cestode eggs in feces and using fecal egg counts of strongylid species of nematodes.

(2) Study Animals: 132 horses, 3 donkeys, and 1 mule, ranging from 9 months to 33 years of age, were randomized to one of two treatment groups. 122 animals were cestode positive on fecal exam prior to enrollment. 85 animals had strongyle fecal egg counts performed prior to enrollment.

(3) Treatment Groups: See Table 4 below.

Table 4: Treatment Groups for Field Study

Treatment Group	Treatment	Total	Cestode +	Strongyle +
1	Vehicle control paste	34	32	20
2	Ivermectin/Praziquantel paste (DUOCARE)	102	90	65

(4) Drug Administration: Treatment was administered orally, as a single dose (200 mcg/kg ivermectin; 2.5 mg/kg praziquantel).

(5) Study Variables: Horses were confirmed to have cestode eggs in fecal samples collected up to 37 days prior to treatment. If strongyles were present in the initial fecal sample, strongyle fecal egg counts were recorded either from that same sample or from a separate sample. Study veterinarians performed physical examinations prior to treatment and at Day 14 or 15 following treatment. Fecal samples were collected and assessed for cestode presence on Day 6, 7, 8, 13, 14, and 15 following treatment. Strongyle fecal egg counts were conducted on approximately Day 14. Owners and personnel conducting treatment administration, physical examinations, and fecal examinations were masked to treatment assignment.

(6) Statistical Methods: For cestodes (praziquantel effectiveness), success rates for week 1 and week 2 were calculated for the test drug treated and vehicle control groups. Parasite presence data were evaluated to detect significant differences between

treated and control groups at week 2 using a generalized linear mixed model. For strongyles (ivermectin effectiveness), strongyle egg counts from fecal samples collected pre-study and on day 14 were analyzed. Log transformed egg counts were evaluated using methods appropriate for repeated measures. Treatment, time, and the interaction between time and treatment were included in the statistical model as fixed effects.

d. Results:

(1) For cestodes, a horse was considered a treatment failure if any of the post-treatment fecal exams (Day 13, 14, 15) were positive for cestode eggs. A horse was considered a treatment success if none of the post-treatment fecal exams (Day 13, 14, 15) were positive for cestode eggs. The results reveal 96% effectiveness under field conditions of use. Statistical analysis of the two treatment groups reveals a significant difference (P<0.0001). See Table 5 below.

Table 5: Results of Cestode Fecal Egg Analysis

	Number of Horses Administered Ivermectin/ Praziquantel (%)	Number of Horses Administered Vehicle Control (%)
Failure	4 (4%)	24 (75%)
Success	86 (96%)	8 (25%)

(2) For strongyles, log transformed fecal egg counts for the treated and control groups were compared. Only 2 horses in the ivermectin/praziquantel treated group were shedding any strongyle eggs on Day 14 post-treatment. All 20 vehicle control horses were still shedding strongyle eggs on Day 14 post-treatment. There was no significant difference between treatment groups in the pre-treatment fecal egg counts (P=0.0885). There was a significant difference between treatment groups at the Day 14 fecal egg counts (P<0.0001). See Table 6 below.

Table 6: Results of Strongyle Fecal Egg Count Analysis

Treatment Group	Pre-treatment Average (epg*)	Post-treatment Average (epg)
Vehicle control	581	439
Ivermectin/Praziquantel	678	<1

*epg=eggs per gram

e. Adverse Reactions: No adverse reactions occurred that were attributed to treatment with DUOCARE.

However, one control horse died during the study. Necropsy revealed multiple pathologic lesions likely due to age. This horse was a vehicle control treated horse and had substantial cestode infection, so was included in the effectiveness database for cestode evaluation as a treatment failure in the vehicle control group.

At one site, it was noted that ascarid eggs were present in treated horses in the post-treatment samples. Since fecal egg counts of ascarid eggs were not performed and ascarids were not present in all horses enrolled in the study, a conclusion on DUOCARE's effectiveness against *Parascaris equorum* could not be made from this study.

f. Conclusion: DUOCARE is safe and effective at treating cestode and strongyle infections when administered at 200 mcg/kg ivermectin and 2.5 mg/kg praziquantel in field conditions.

4. Bioequivalence to ivermectin paste 1.87% (NADA 134-314)

a. The formulation of this combination product is based on the formulation of an approved abbreviated NADA (ANADA) for ivermectin paste 1.87% (ANADA 200-564). In that application, the ivermectin paste 1.87% formulation was determined to be bioequivalent to the approved ivermectin paste 1.87% (NADA 134-314). The determination of bioequivalence to the approved ivermectin paste, in combination with the data summarized above, provides substantial evidence of effectiveness for the ivermectin/praziquantel combination product for all additional indications approved under NADA 134-314.

III. TARGET ANIMAL SAFETY:

A. Type of Study: Target Animal Safety Study

1. Title: Target Animal Safety Evaluation of Ivermectin & Praziquantel Oral Gel in Horses (Study No. 145-2-775-1001, Sept. 2005-Oct. 2005)
2. Study Director: Craig Reinemeyer, DVM, PhD
   East Tennessee Clinical Research, Inc.
3. Study Design:
   a. Objective: The information obtained in this study was collected to document, 1) safety of the combination drug product under the conditions of recommended use, 2) signs associated with toxicity of the drug and 3) margin of safety of the drug product.
   b. Study Animals: The animals were healthy, intact male and female foals of typical American breeds (Quarter Horses, Paint Horses, Tennessee Walking Horses, and grades) aged 153-189 days and weighing 115-218 kg.
   c. Experimental Design: This was a single-facility, non-clinical, parallel study involving the administration of one, three, and five times the recommended dose. Animals were blocked (n=4) according to weight within sex, and treatments were randomly assigned to each block. Controls were untreated. Test-article treated groups were administered an oral

paste (the formulation intended for commercial marketing), at the rates listed in Table 7 below.

Table 7. Treatment Groups in the Target Animal Safety Study

Group	Number of Animals [a]	Treatment Type [b]	Dosage	Route	Frequency [c]
1	3 m, 3 f	Control	*	N/A	N/A
2	3 m, 3 f	Test (1X)	0.2 mg/kg ivermectin 2.5 mg/kg praziquantel	Oral	Once a day for 4 consecutive days
3	3 m, 3 f	Test (3X)	0.6 mg/kg ivermectin 7.5 mg/kg praziquantel	Oral	Once a day for 4 consecutive days
4	3 m, 3 f	Test (5X)	1.0 mg/kg ivermectin 12.5 mg/kg praziquantel	Oral	Once a day for 4 consecutive days

[a] Weaned intact male and female foals.
[b] Test article = DUOCARE paste (18.7 mg ivermectin & 233.75 mg praziquantel per gram paste).
[c] 4 consecutive days were study Days 0,1, 2, and 3.
* Control animals untreated.

d. Drug Administration: Animals in group 1 (control) did not receive treatment. Animals in groups 2, 3, and 4 were administered the assigned treatment once daily for 4 consecutive days.
e. Measurements and Observations: Each animal received a physical examination on Days -1, 3, and again prior to euthanasia (on Day 14, 15, or 16). Body weights were measured on Days -1, 3, and again prior to euthanasia (on Day 14, 15, or 16). Clinical observations were conducted once daily during the first week of acclimation and then twice daily from acclimation Day -7 through the remainder of the study. Clinical observations included an assessment of general appearance, behavior/attitude, appetite, and fecal consistency. Additional clinical observations were made hourly for 6 hours after each dosing on Days 0 through 3, starting 1 hour after the last foal was treated. Oral cavity observations of each foal were observed once daily on Days -1 through necropsy. Peripheral blood samples were collected for clinical pathology testing (serum chemistry, hematology, PT and PTT) from each foal prior to enrollment (Day -6), on Day 3, and again prior to euthanasia on Day 14, 15, or 16. On study Days 14, 15, or 16 all foals in the study were euthanized (8 foals each day), and subjected to postmortem examination. Histopathological examinations were performed on harvested tissues from all foals in all treatment groups.

4. Statistical Methods: Numerical physical examination data and clinical pathology values were examined as a single time point and over time. To evaluate the data as a single time point, an analysis of variance was used to evaluate the fixed effects of gender, dose, and the gender by dose interaction.

To assess the effects over time, an analysis of variance model appropriate for repeated measures was used. Time and all interactions with time were included as fixed effects. For both analyses, weight within sex was included as a random effect and when available, pre-treatment values were included as covariates. The three-way interaction of dose by gender by time was evaluated at $\alpha=0.05$; all other effects were evaluated at $\alpha=0.1$. When appropriate, pairwise comparisons were made using an unadjusted $\alpha=0.1$.

5. Results:
   a. Physical Examinations – No physical exam abnormalities were attributed to test article administration. Transient or incidental findings during the study included nasal discharge, ocular discharge, cough, and abnormal feces encountered prior to treatment as well as during the study period. The foals in this study had been recently weaned and transported. Additionally, histology findings summarized below suggest probable *Streptococcus equi* (strangles) infection in some of the enrolled foals which could also account for such findings.
   b. Body Weights – No dose related differences in body weights were found. Most foals lost a small amount of weight between initial treatment and Day 3 measurements. However, by the time of euthanasia most treated foals had returned to or exceeded their pre-treatment weight.
   c. Clinical Observations – One foal in the 3X group had a colic event on study Day 8 (5 days after the last dose of test article was administered). The event was characterized by pale mucous membranes, a temperature of 98.3º F, lethargy, lying down, attempts to roll occasionally, and lack of interest in offered grain and hay. The event resolved without treatment.
      Other transient or incidental findings during the study were consistent with the observations in the physical examinations including nasal discharge, ocular discharge, cough, and abnormal feces encountered prior to treatment as well as during the study period. Additionally, as described above in the physical examination findings, these could be attributed to a probable *Streptococcus equi* (strangles) infection in some of the foals.
   d. Oral Cavity Observations – No test article-related abnormal signs were revealed during oral cavity observations. Transient findings of minor gingival erythema and abrasion were recorded during the study for both treated and untreated animals.
   e. Clinical Pathology (hematology, biochemical and coagulation parameters) – Although occasional individual clinical pathology values were outside reference ranges for the equine species, none were considered an adverse response to treatment.
   f. Gross and Microscopic Pathology – As described in the clinical observations section above, a single 3X foal exhibited signs of colic on study Day 8. Post-mortem examination of this foal revealed a lesion that, on gross and microscopic examination, was described as an ulcerative lesion of the ventral colon.
      Other prevalent abnormalities were attributable to probable *Streptococcus equi* (strangles) infection in some enrolled foals. Associated lesions included follicular pharyngitis, retropharyngeal abscesses, and one septic carpal joint that may have been infected hematogenously by *Streptococcus equi*. Although sporadic microscopic abnormalities were observed in various tissues of foals from all treatment groups, none were considered an adverse response to treatment.

6. Adverse Reactions: There were no test-article related findings observed in this study during clinical observations or physical examinations.
7. Conclusions: DUOCARE was safe in 5 to 6 month old foals treated with up to 5 times the label dosage for 4 consecutive days.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in horses. 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.

The product labeling contains the following Warning statement: "Do not use in horses intended for human consumption."

V. USER SAFETY:

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

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

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 DUOCARE, when used according to the label, is safe and effective for the treatment and control of gastrointestinal nematodes, cestodes, and bots in horses over 5 months of age.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

DUOCARE, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate effectiveness and safety of DUOCARE.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.