

Date of Approval: SEP 15 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-227

ULCERGARD

omeprazole

For the prevention of gastric ulcers in horses

Sponsored by:

Merial Ltd.
3239 Satellite Blvd.
Duluth, GA 30096

2006-141-227

FOIS2

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1. GENERAL INFORMATION:

- a. File Number: NADA 141-227
- b. Sponsor: Merial Ltd.
3239 Satellite Blvd., Bldg. 500,
Duluth, GA 30096 - 4640

Drug Labeler Code: 050604
- c. Established Name: omeprazole
- d. Proprietary Name: ULCERGARD
- e. Dosage Form: An oral paste containing 37% w/w omeprazole
- f. How Supplied: The paste comes in a 4-dose oral syringe with individual doses marked 1 - 4
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: Each syringe contains 2.28 g of omeprazole
- i. Route of Administration: Oral
- j. Species/Class: Equine
- k. Recommended Dosage: The minimum recommended dosage is 1 mg/kg per day (0.45 mg/lb) or ¼ syringe. When given once daily during the stressful period, ULCERGARD has been shown to effectively prevent stomach ulcers in horses. This effect was tested in horses exposed to stressful conditions for either 8 or 28 days. Horses over 1200 pounds body weight should receive two doses once per day.
- l. Pharmacological Category: Anti-ulcer medication
- m. Indications: For the prevention of gastric ulcers in horses
- n. Effect of Supplement: To change the DOSAGE section to include an 8 day treatment duration, to clarify the dosage chart, and to change the storage conditions

2. **EFFECTIVENESS:**

a. **Dosage Characterization:**

“Studies to Determine the Effectiveness of Omeprazole Oral Paste for the Prevention of Occurrence of Gastric Ulcers in Horses Under Field Conditions” (PR&D 0057301, PR&D 0057302 and PR&D 0057303)

Investigators:

Michèle Doucet, DVSc, Gary W. White, DVM, and Roger Sifferman, DVM

Study Locations:

Centre d'Entraînement Des Chênes
St. Basile le Grand, Québec, Canada

Rex Brooks Training Stables
Vian, OK

Centre d'Entraînement Tourigny
Bécancour, Québec, Canada

Los Alamitos Race Track
Los Alamitos, CA

Les Écuries Alain Durivage
(Écuries AD Stable)
Chambly, Québec, Canada

Blane Schvaneveldt Ranch
Romoland, CA

Animals: Sixty Quarter horses and 35 Standardbred horses (20 males, 20 male castrates and 55 females) ranging in age from 2 - 6 years with a body weight range of 696 - 1250 lbs were enrolled. Horses were free of gastric ulcers as confirmed by endoscopy prior to enrollment. Horses were managed in individual stalls and daily training regimen consistent with ulcerogenic conditions throughout the study period. Ninety-two horses completed the study.

Treatment Groups: Within each study, replicates of five horses were formed based on breed, gender, age, location and/or training level. Within replicate, horses were randomly allocated to one of five treatment groups. Group 1 was sham-dosed with an empty syringe from Day 0 - 27. Group 2 received 1 mg/kg/day omeprazole and Group 3 received 2 mg/kg/day omeprazole from Day 0 - 27. To evaluate the effect of a loading dose, Groups 4 and 5 were initially given 4 mg/kg/day of omeprazole from Day 0 - 3. On Day 4 - 27, Group 4 horses were given omeprazole at 1 mg/kg/day and Group 5 horses were given omeprazole at 2 mg/kg/day.

Route of Administration: Oral

Duration of Study: 28 days

Measurements: The stomach of each horse was examined endoscopically prior to enrollment to confirm that horses were free of gastric ulcers. Follow up endoscopic examinations were conducted on Day ~28. For each horse, the

endoscopist recorded a score for the most severe stomach lesions. The following scoring system for gastric ulcers was used:

- 0 Intact mucosal epithelium (can have reddening and/or hyperkeratosis)
- 1 Small single or small multifocal lesion
- 2 Large single or large multifocal lesion
- 3 Extensive (often coalescing) lesions with areas of apparent deep ulceration

Statistical Methods: All horses were ulcer-free at the beginning of the study (ulcer score = 0). Although horses with observed ulcers on Day 28 were given a score based on ulcer severity, for statistical purposes any horse that scored ≥ 1 was considered a treatment failure and horses that remained ulcer-free on Day 28 (ulcer score = 0) were considered a treatment success.

Study Results:

Table 1. PR&D 0057301, PR&D 0057302 and PR&D 0057303

Treatment	n	Success	Failure
Group 1 Sham-dosed (Days 0 - 27/28)	17	4 (24%)	13 (76%)
Group 2 Omeprazole 1 mg/kg/day (Days 0 - 27/28)	19	16 (84%)	3 (16%)
Group 3 Omeprazole 2 mg/kg/day (Days 0 - 27/28)	18	16 (89%)	2 (11%)
Group 4 Omeprazole 4 mg/kg/day (Days 0 - 3) 1 mg/kg/day (Days 4 - 27/28)	19	15 (79%)	4 (21%)
Group 5 Omeprazole 4 mg/kg/day (Days 0 - 3) 2 mg/kg/day (Days 4 - 27/28)	19	15 (79%)	4 (21%)

Observations: No adverse events related to omeprazole treatment were reported in these studies. The paste was accepted by all of the omeprazole-treated horses.

Conclusions: Omeprazole given at 1 mg/kg/day for 28 days was as effective as 2 mg/kg/day in the prevention of gastric ulcers in ulcer-free horses. Additionally,

omeprazole given at 1 mg/kg/day for 28 days was as effective in the prevention of gastric ulcers in horses as a regimen that included an initial 4-day loading dose of 4 mg/kg/day followed by 24 days of omeprazole at 1 mg/kg/day. A dose of 1 mg/kg was determined to be the effective dose.

b. Substantial Evidence:

- 1) Study to Determine the Efficacy of Omeprazole 37% Oral Paste for the Prevention of Occurrence of Gastric Ulcers in Horses under Field Conditions for a Short Period of Time (PR&D 0119101, PR&D 0119102, PR&D 0119103).

Investigators:

Gary W. White, DVM, Scott McClure, DVM, and Roger Sifferman, DVM

Study Locations:

Brian Muse Stables
Sallisaw, OK

Dave McShane Racing Stables
Maxwell, Iowa

Rex Brooks Stables
Sallisaw, OK

Gonzales Training Stables
Cameron, TX

Animals: The details on the animals enrolled in the study are provided in Table 2, below:

Table 2. Enrolled Animals

Study Site	Breed	Number of Animals	Sex	Weight Range	Age (years)
PR&D 0119101	Quarter horses	40	14 Mares 8 Stallions 18 Geldings	775 – 1105 lbs (352 – 502 kg)	2 to 3
PR&D 0119102	Thoroughbreds	30	14 Mares 16 Geldings	974 – 1239 lbs (442 – 562 kg)	2 to 10
PR&D 0119103	Quarter horses	32	12 Mares 6 Stallions 14 Geldings	678 – 1192 lbs (308 – 542 kg)	1 to 9

Four horses (one sham-dosed and three omeprazole-treated) were excluded from the effectiveness analysis because they were given flunixin meglumine during the study.

Study design: The study was conducted as a multi-center, randomized block design (PR&D 0119101, 0119102, and 0119103). Control horses were sham-dosed. All horses had gastric ulcer scores of zero (i.e., no gastric ulcers) on Day 0 as confirmed by gastroscopy performed on Day -2 or Day -1. For the duration of the study, horses were held in an ulcerogenic environment (confined individual

housing with daily training). The training regimen was the same for all horses in a given replicate on all study days. The training regimens and the type of individual housing varied between study sites and, in some cases, between replicates.

Treatment Groups: At each study site, replicates of horses were formed based on similarity of breed, gender, and age. Within these replicates the horses were randomly allocated to one of two treatment groups (sham-dosing with an empty syringe or oral administration of omeprazole paste at 1 mg/kg/day). Horses were treated once daily for 8 days (Days 0 - 7).

Route of Administration: Oral

Duration of Study: 8 days

Measurements: Examination of the stomach via endoscopy was conducted for each horse on Day -2 or Day -1 to confirm the absence of gastric ulcers (ulcer score = 0). Follow-up endoscopic exams were conducted again on all horses on Day 7 (*i.e.*, post-treatment on the last day of treatment). For each horse, the endoscopist recorded a score for the worst stomach lesions observed according to the following scoring system:

- 0 Intact mucosal epithelium (can have reddening and/or hyperkeratosis)
- 1 Small single or small multifocal lesion
- 2 Large single or large multifocal lesion
- 3 Extensive (often coalescing) lesions with areas of deep ulceration

Horses with observed ulcers on Day 7 were given a score based on ulcer severity; however, any horse that scored ≥ 1 was considered a treatment failure. Horses that remained ulcer-free on Day 7 (ulcer score = 0) were considered treatment successes.

Statistical Methods: The primary effectiveness variable was treatment success, defined as the absence of gastric ulcers (ulcer score = 0) at Day 7. The overall treatment effects were tested using a one-sided test under a generalized linear mixed model applied to the binary response. The model included treatment as a fixed effect and site and site*treatment as random effects. Within each site, the treatment groups were compared using Fisher's Exact test.

Results: The one - sided overall test for treatment differences had a p-value of $p = 0.05$. Within each site, the test for treatment differences using one-sided Fisher's Exact test had p-values of $p \leq 0.05$. The success rates by site are summarized in Table 3, below.

Table 3. Treatment success rates by study site

Study Site	Sample Size	Number (%) of Successes ^a		P-value ^b
		Control	Omeprazole	
PR&D 0119101	37	10/19 (53%)	15/18 (83%)	0.05
PR&D 0119102	30	4/15 (27%)	15/15 (100%)	< 0.01
PR&D 0119103	31	0/16 (0%)	12/15 (80%)	< 0.01
All sites	98	14/50 (28%)	42/48 (87%)	0.05

^a Horses with gastric lesion score = 0 at Day 7.

^b One-sided p-values for testing the difference between control and omeprazole groups. The Fisher's Exact test was used for each site and the generalized linear mixed model was used for the overall test across sites.

Observations: One horse treated with omeprazole experienced colic that responded to medical therapy (flunixin meglumine and mineral oil). The horse continued on omeprazole therapy for the duration of the study.

Conclusions: These data confirm that omeprazole at 1 mg/kg/day for 8 days was effective in the prevention of gastric ulcers in horses exposed to ulcerogenic conditions (individual housing and daily training).

- 2) Studies to Determine the Effectiveness of Omeprazole Oral Paste for the Prevention of Gastric Ulcers in Horses Under Field Conditions (PR&D 0048601, PR&D 0048603 and PR&D 0048604)

Investigators:

William Bernard, DVM, Gary W. White, DVM, and Scott McClure, DVM

Study Locations:

Kentucky Training Center
Lexington, KY

Rex Brooks Training Stables
Sallisaw, OK

Dave McShane Racing Stables
Maxwell, IA

Animals: Fifty-six Thoroughbreds and 24 Quarter horses (40 females, 20 males and 20 male castrates) ranging in age from 1 - 7 years and body weight range of 688 - 1223 lbs were enrolled. Horses were free of gastric ulcers as confirmed by endoscopy prior to enrollment. Horses were managed in individual stalls and daily

training regimens consistent with ulcerogenic conditions throughout the study period. Seventy-seven horses completed the study.

Treatment Groups: Within each study, replicates of two horses were formed based on similarities in age and/or gender. Within each replicate, horses were randomly allocated to receive either sham-dosing with an empty syringe or omeprazole at 1 mg/kg/day from Day 0 - 27.

Route of administration: Oral

Duration of Study: 28 days

Measurements: The stomach of each horse was examined endoscopically prior to enrollment to confirm that horses were free of gastric ulcers. Follow-up endoscopic examinations were conducted on Day 28 of treatment. For each horse, the endoscopist recorded a score for the most severe stomach lesions. The same gastric ulcer scoring system outlined above in Section 2.a. was used in these studies.

Statistical Methods: All horses were ulcer-free at the beginning of the study (ulcer score = 0). Although horses with observed ulcers on Day 28 were given a score based on ulcer severity, for statistical purposes any horse that scored ≥ 1 was considered a treatment failure and horses that remained ulcer-free on Day 28 (ulcer score = 0) were considered a treatment success.

Results:

Table 4. PR&D 0048601, PR&D 0048603 and PR&D 0048604

Treatment	n	Success	Failure
Group 1 Sham - dosed (Days 0 - 28)	39	4 (10%)	35 (90%)
Group 2 Omeprazole 1 mg/kg/day (Days 0 - 28)	38	31 (82%)	7 (18%)

Observations: No adverse events related to omeprazole treatment were reported in these studies. The paste was accepted by all of the omeprazole-treated horses.

A combined analysis of the three dose confirmation studies and the three dose determination studies is illustrated in Table 5.

Table 5. Combined analysis

Study	Sham - dosed Success	Sham - dosed Failure	Sham - dosed Total	Treatment success 1 mg/kg/day	Treatment failure 1 mg/kg/day	Treatment Total 1 mg/kg/day	Total
0048601	2	12	14	11	2	13	27
0048603	0	12	12	10	2	12	24
0048604	2	11	13	10	3	13	26
Combined Dose Confirmation	4 (10%)	35 (90%)	39 (100%)	31 (82%)	7 (18%)	38 (100%)	77
0057301	2	4	6	7	0	7	13
0057302	0	6	6	4	2	6	12
0057303	2	3	5	5	1	6	11
Combined Dose Determination	4 (24%)	13 (76%)	17 (100%)	16 (84%)	3 (16%)	19 (100%)	36
Total	8 (14%)	48 (86%)	56 (100%)	47 (82%)	10 (18%)	57 (100%)	113

The primary effectiveness variable for this combined analysis is the binomial variable, presence of ulcers observed. A generalized linear mixed effects model (“glimmix”) analysis with a binomial error and a logit link was used. Treatment was a fixed effect. We included block, study and study by treatment as random effects in our analysis. The glimmix analysis showed that the treatments (sham-dose versus omeprazole) were significantly different at $p < 0.0001$.

Conclusions: These data confirm that omeprazole at 1 mg/kg/day for 28 days was effective in the prevention of gastric ulcers in horses exposed to ulcerogenic conditions.

3. TARGET ANIMAL SAFETY:

Please refer to the NADA 141-123 FOI Summary for GASTROGARD (omeprazole) Paste for Horses dated March 16, 1999.

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.

Human Warnings are provided on the product label as follows: “Not for use in humans. Keep this and all medications out of the reach of children. In case of ingestion by humans, contact a physician. **Do not use in horses intended for human consumption.**”

5. 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 of the implementing regulations. The data demonstrate that ULCERGARD when used under the labeled conditions of use is safe and effective for the prevention of gastric ulcers in horses.

The drug is available over-the-counter for lay use because a diagnosis of gastric ulcer disease is not required for use of the drug to prevent the disease.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new indication, an 8 day treatment duration, for which this supplement is approved. This is based on new effectiveness study data that establishes the effectiveness of omeprazole at 1 mg/kg/day for 8 days for the prevention of gastric ulcers in horses.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

ULCERGARD is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
5708017	April 4, 2015
6939881 B2	May 29, 2021

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

Two approved presentations:

- A. Traditional tuck carton with package "outsert" and syringe label
- B. Extended - tuck carton with syringe label

3.937

1.771

Unvarnished & unprinted area at top for overcap
3-15/16" W x 1-4" H
Also not to be printed in this area

UlcerGard™
(omeprazole) Oral Paste for Horses

INDS: For the prevention of gastric ulcers in horses.
READ CARTON LABEL FOR FURTHER INSTRUCTIONS AND IMPORTANT INFORMATION.

WARNING: Not for use in humans. Keep this and all medical kits out of the reach of children in case of ingestion by humans. Consult a physician. Do not use in horses intended for human consumption.

Net Wt. 6.15 g (2.28 g of omeprazole)

STORAGE: Store at 68°F-77°F (20-25°C). Excursions between 59°F-86°F (15-30°C) are permitted.

ULCERGARD™ is a trademark of the AstraZeneca Group of Companies.
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Lot:  Unvarnished & unprinted area
1-7/16" W x 5/16" H

Merial is a Merck Company
3121 Sankar Blvd. Duluth, GA 30096-6640
6014-1001-1117-01 Rev. 02/06



