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Stomach Ulcers Identified in 86 Percent of Harness Racers *Nationwide events demonstrate all horses at risk for stomach ulcers*

DULUTH, GA. — May 13, 2009 — In gastroscopy events at veterinary clinics and university campuses across the country, 86 percent of harness racing horses were identified with stomach ulcers.¹

“At these events, veterinarians evaluated the horses’ stomachs using gastroscopy, which is the only definitive way to determine if a horse has ulcers,” says April Knudson, DVM, manager, Veterinary Services, Merial. “I traveled the country to attend many of these events myself, and one thing is for certain — stomach ulcers can occur in horses of all breeds and disciplines.”

Throughout the year, 658 horses in 25 states participated in events. Overall, 60 percent — 397 horses — had some ulceration as identified by gastroscopy. Horses of varying breeds, ages and previous ulcer histories were found to have stomach ulcers, including:¹

- Horses from 1 to 41 years old
- Breeds from ponies to Percherons
- Horses kept in box stalls and in pastures
- Those in training and horses rarely ridden

“These results demonstrate how stomach ulcers can occur in any horse,” Dr. Knudson says. “Even the best-cared-for horses can suffer from this condition. For horses that compete, like harness racing horses, stomach ulcers could keep them from performing at their best, too.”

There are many triggers for stomach ulcer development, and stress is an important contributing factor. Horses are especially sensitive and may experience stress when exposed

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to situations you would think of as normal, including: competition, training, travel, lay-up due to sickness or injury, shows or events, limited turnout or grazing, or trailering.^{2,3}

Ulcers can develop quickly, too. One study showed that horses can develop stomach ulcers in as little as five days.⁴

Before stressful events, a once-daily dose of ULCERGARD® (omeprazole) has been proven effective in preventing stomach ulcers over both short and long periods of time.^{*,5} ULCERGARD is the only FDA-approved, proven preventive for stomach ulcers.

“For competitive horse owners, it’s important to think about preventing stomach ulcers before an unexpected trip to the veterinarian is required,” Dr. Knudson notes. “If horses have been exposed to stressful situations and are at risk for stomach ulcers, a veterinarian may be able to provide a presumptive diagnosis without gastroscopy.”

If a veterinarian diagnoses stomach ulcers, one tube of GASTROGARD® (omeprazole) given once per day for 28 days effectively heals or reduces the severity of gastric ulcers.⁶ GASTROGARD is the only product FDA-approved to treat and heal stomach ulcers.

“With proven products like these, there is no reason that a horse needs to suffer from stomach ulcers,” Dr. Knudson says. “Ask your veterinarian if your horse is at risk for stomach ulcers or if there are scoping events in the area.”

Merial is a world-leading, innovation-driven animal health company, providing a comprehensive range of products to enhance the health, well-being and performance of a wide range of animals. Merial employs approximately 5,400 people and operates in more than 150 countries worldwide. Its 2008 sales were over \$2.6 billion. Merial Limited is a joint venture between Merck & Co., Inc. and sanofi-aventis. For more information, please see www.merial.com.

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Federal (USA) law restricts GASTROGARD to use by or on the order of a licensed veterinarian. GASTROGARD is indicated for the treatment and prevention of recurrence of gastric ulcers in horses and foals 4 weeks and older. In an efficacy trial, no adverse reactions were observed. Safety in pregnant or lactating mares has not been determined. For more information, visit www.gastrogard.com.

ULCERGARD can be used in horses that weigh at least 600 pounds. The effectiveness of ULCERGARD in the prevention of gastric ulcers in foals and weanlings has not been evaluated. ULCERGARD may be used safely in breeding stallions. Safety in pregnant mares has not been determined.

*When treated for 8 or 28 days, ULCERGARD is proven to effectively prevent stomach ulcers in horses exposed to stressful conditions.

¹Data on file at Merial.

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²ULCERGARD product label.

³Murray MJ. Disorders of the stomach. In: Smith BP, ed. *Large Animal Internal Medicine*. St. Louis; CV Mosby, 1990: 710-717.

⁴McClure SR, Carithers DS, Gross SJ, Murray MJ. Gastric ulcer development in horses in a simulated show or training environment. *J Am Vet Med Assoc* 2005; 227(5): 775-777.

⁵Freedom of Information summary for ULCERGARD Oral Paste.

⁶GASTROGARD Oral Paste product label.

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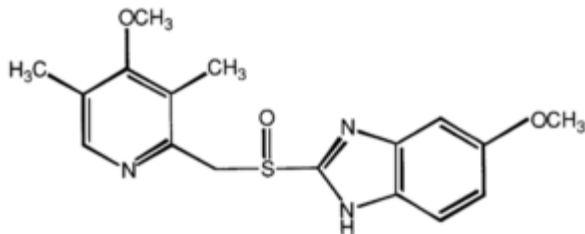
GASTROGARD® (omeprazole)
Oral Paste for Horses and Foals
NADA 141-123, Approved by FDA

Caution

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description

Chemical name: 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl] methyl]sulfinyl]-1 H-benzimidazole. Empirical formula: C₁₇H₁₉N₃O₃S. Molecular weight: 345.42. Structural formula:



How Supplied

GASTROGARD® (omeprazole) Paste for horses contains 37% w/w omeprazole and is available in an adjustable-dose syringe. Each syringe contains 2.28 g of omeprazole. Syringes are calibrated according to body weight and are available in boxes of 7 units or 72 units.

Storage Conditions

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

Indications

For treatment and prevention of recurrence of gastric ulcers in horses and foals 4 weeks of age and older.

Dosage Regimen

For treatment of gastric ulcers, GASTROGARD Paste should be administered orally once-a-day for 4 weeks at the recommended dosage of 1.8 mg omeprazole/lb body weight (4 mg/kg). For the prevention of recurrence of ulcers, continue treatment for at least an additional 4 weeks by administering GASTROGARD Paste at the recommended daily maintenance dose of 0.9 mg/lb (2 mg/kg).

Directions for Use

GASTROGARD Paste for horses is recommended for use in horses and foals 4 weeks of age and older. The contents of one syringe will dose a 1250 lb (568 kg) horse at the rate of 1.8 mg omeprazole/lb body weight (4 mg/kg). For treatment of gastric ulcers, each weight marking on the syringe plunger will deliver sufficient omeprazole to treat 250 lb (114 kg) body weight. For prevention of recurrence of gastric ulcers, each weight marking will deliver sufficient omeprazole to dose 500 lb (227 kg) body weight.

To deliver GASTROGARD Paste at the treatment dose rate of 1.8 mg omeprazole/lb body weight (4 mg/kg), set the syringe plunger to the appropriate weight marking according to the horse's weight in pounds.

To deliver GASTROGARD Paste at the dose rate of 0.9 mg/lb (2 mg/kg) to prevent recurrence of ulcers, set the syringe plunger to the weight marking corresponding to half of the horse's weight in pounds.

To set the syringe plunger, unlock the knurled ring by rotating it 1/4 turn. Slide the knurled ring along the plunger shaft so that the side nearest the barrel is at the appropriate notch. Rotate the plunger ring 1/4 turn to lock it in place and ensure it is locked. Make sure the horse's mouth contains no feed. Remove the cover from the tip of the syringe, and insert the syringe into the horse's mouth at the interdental space. Depress the plunger until stopped by the knurled ring. The dose should be deposited on the back of the tongue or deep into the cheek pouch. Care should be taken to ensure that the horse consumes the complete dose. Treated animals should be observed briefly after administration to ensure that part of the dose is not lost or rejected. If any of the dose is lost, redosing is recommended.

If, after dosing, the syringe is not completely empty, it may be reused on following days until emptied. Replace the cap after each use.

Warning

Do not use in horses intended for human consumption. Keep this and all drugs out of the reach of children. In case of ingestion, contact a physician. Physicians may contact a poison control center for advice concerning accidental ingestion.

Adverse Reactions

In efficacy trials, when the drug was administered at 1.8 mg omeprazole/lb (4 mg/kg) body weight daily for 28 days and 0.9 mg omeprazole/lb (2 mg/kg) body weight daily for 30 additional days, no adverse reactions were observed.

Precautions

The safety of GASTROGARD Paste has not been determined in pregnant or lactating mares.

Clinical Pharmacology

Mechanism of Action: Omeprazole is a gastric acid pump inhibitor that regulates the final step in hydrogen ion production and blocks gastric acid secretion regardless of the stimulus. Omeprazole irreversibly binds to the gastric parietal cell's H⁺, K⁺ ATPase enzyme which pumps hydrogen ions into the lumen of the stomach in exchange for potassium ions. Since omeprazole accumulates in the cell canaliculi and is irreversibly bound to the effect site, the plasma concentration at steady state is not directly related to the amount that is bound to the enzyme. The relationship between omeprazole action and plasma concentration is a function of the rate-limiting process of H⁺, K⁺ ATPase activity/turnover. Once all of the enzyme becomes bound, acid secretion resumes only after new H⁺, K⁺ ATPase is synthesized in the parietal cell (i.e., the rate of new enzyme synthesis exceeds the rate of inhibition).

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Pharmacodynamics: In a study of pharmacodynamic effects using horses with gastric cannulae, secretion of gastric acid was inhibited in horses given 4 mg omeprazole/kg/day. After the expected maximum suppression of gastric acid secretion was reached (5 days), the actual secretion of gastric acid was reduced by 99%, 95% and 90% at 8, 16, and 24 hours, respectively.

Pharmacokinetics: In a pharmacokinetic study involving thirteen healthy, mixed breed horses (8 female, 5 male) receiving multiple doses of omeprazole paste (1.8 mg/lb once daily for fifteen days) in either a fed or fasted state, there was no evidence of drug accumulation in the plasma when comparing the extent of systemic exposure ($AUC_{0-\infty}$). When comparing the individual bioavailability data ($AUC_{0-\infty}$, C_{max} , and T_{max} measurements) across the study days, there was great inter- and intrasubject variability in the rate and extent of product absorption. Also, the extent of omeprazole absorption in horses was reduced by approximately 67% in the presence of food. This is evidenced by the observation that the mean ($AUC_{0-\infty}$) values measured during the fifth day of omeprazole therapy when the animals were fasted for 24 hours was approximately three times greater than the AUC estimated after the first and fifteenth doses when the horses were fed hay ad libitum and sweet feed (grain) twice daily. Prandial status did not affect the rate of drug elimination. The terminal half-life estimates (N=38) ranged from approximately one-half to eight hours.

Efficacy

Dose Confirmation: *GASTROGARD*[®] (omeprazole) Paste, administered to provide omeprazole at 1.8 mg/lb (4 mg/kg) daily for 28 days, effectively healed or reduced the severity of gastric ulcers in 92% of omeprazole-treated horses. In comparison, 32% of controls exhibited healed or less severe ulcers. Horses enrolled in this study were healthy animals confirmed to have gastric ulcers by gastroscopy. Subsequent daily administration of *GASTROGARD* Paste to provide omeprazole at 0.9 mg/lb (2 mg/kg) for 30 days prevented recurrence of gastric ulcers in 84% of treated horses, whereas ulcers recurred or became more severe were in horses removed from omeprazole treatment.

Clinical Field Trials: *GASTROGARD* Paste administered at 1.8 mg/lb (4 mg/kg) daily for 28 days healed or reduced severity of gastric ulcers in 99% of omeprazole-treated horses. In comparison, 32.4% of control horses had healed ulcers or ulcers which were reduced in severity. These trials included horses of various breeds and under different management conditions, and included horses in race or show training, pleasure horses, and foals as young as one month. Horses enrolled in the efficacy trials were healthy animals confirmed to have gastric ulcers by gastroscopy. In these field trials, horses readily accepted *GASTROGARD* Paste. There were no drug related adverse reactions. In the clinical trials, *GASTROGARD* Paste was used concomitantly with other therapies, which included: anthelmintics, antibiotics, non-steroidal and steroidal anti-inflammatory agents, diuretics, tranquilizers and vaccines.

Diagnostic and Management Considerations: The following clinical signs may be associated with gastric ulceration in adult horses: inappetence or decreased appetite, recurrent colic, intermittent loose stools or chronic diarrhea, poor hair coat, poor body condition, or poor performance. Clinical signs in foals may include: bruxism (grinding of teeth), excess salivation, colic, cranial abdominal tenderness, anorexia, diarrhea, sternal recumbency or weakness. A more accurate diagnosis of gastric ulceration in horses and foals may be made if ulcers are visualized directly by endoscopic examination of the gastric mucosa.

Gastric ulcers may recur in horses if therapy to prevent recurrence is not administered after the initial treatment is completed. Use *GASTROGARD* Paste at 0.9 mg omeprazole/lb body weight (2 mg/kg) for control of gastric ulcers following treatment. The safety of administration of *GASTROGARD* Paste for longer than 91 days has not been determined.

Maximal acid suppression occurs after three to five days of treatment with omeprazole.

Safety

- *GASTROGARD* Paste was well tolerated in the following controlled efficacy and safety studies.
- In field trials involving 139 horses, including foals as young as one month of age, no adverse reactions attributable to omeprazole treatment were noted.
- In a placebo controlled adult horse safety study, horses received 20 mg/kg/day omeprazole (5x the recommended dose) for 90 days. No treatment related adverse effects were observed.
- In a placebo controlled tolerance study, adult horses were treated with *GASTROGARD* Paste at a dosage of 40 mg/kg/day (10x the recommended dose) for 21 days. No treatment related adverse effects were observed.
- A placebo controlled foal safety study evaluated the safety of omeprazole at doses of 4, 12 or 20 mg/kg (1, 3, or 5x) once daily for 91 days. Foals ranged in age from 66 to 110 days at study initiation. Gamma glutamyltransferase (GGT) levels were significantly elevated in horses treated at exaggerated doses of 20 mg/kg (5x the recommended dose). Mean stomach to body weight ratio was higher for foals in the 3x and 5x groups than for controls; however, no abnormalities of the stomach were evident on histological examination.

Reproductive Safety

In a male reproductive safety study, 10 stallions received *GASTROGARD* Paste at 12 mg/kg/day (3x the recommended dose) for 70 days. No treatment related adverse effects on semen quality or breeding behavior were observed. A safety study in breeding mares has not been conducted.

For More Information

Please call 1-888-637-4251 and please visit our web site at www.gastrogard.com.

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