Equine gastric ulcer syndrome (EGUS) is the term commonly used to describe ulcers or erosive lesions in the stomach of the horse, but we now differentiate it into two diseases depending on where the lesions occur: equine squamous gastric disease (ESGD) and equine glandular gastric disease (EGGD). Ongoing work shows that the diseases have overlapping yet distinct pathophysiology, risk factors and prevalence; however, until somewhat recently, recommendations for treatment of EGUS have not differentiated between the two diseases. Improved recognition of the difficulty in treating EGGD has resulted in modified treatment protocols.

ESGD occurs when the unprotected squamous mucosa has increased duration of contact with acid. EGGD occurs due to a combination of acid injury and failure of the normal protective mechanisms. Therefore, suppression of acid production remains the cornerstone for treatment of ESGD, but only part of the treatment for EGGD. While it has been shown that monotherapy with omeprazole at 4 mg/kg for 28 days will effectively heal or reduce the severity of squamous ulcers in 92% of cases, new evidence suggests that only 9-32% of glandular lesions are healed with a similar dosing regimen.

ACID SUPPRESSION

The goal of acid suppression is to increase the stomach pH to greater than 4.0 for at least 16 hours per day, which should allow normal healing. There are three approaches to acid suppression: proton pump inhibitors (omeprazole), histamine receptor antagonists (ranitidine) and antacids.

Omeprazole binds irreversibly to the proton pump in the parietal cells of the glandular fundus, and inhibits transport of hydrogen ions into the stomach. It is that irreversible binding that allows the convenience of once-a-day dosing.[1] The standard label duration of treatment for ESGD is 28 days; however, that may be longer or shorter, depending on the severity of ulcers and the ability to make substantive management changes. Omeprazole needs to be administered in a protected formulation, as it must make it through the acidic stomach to the small intestine, where it is absorbed and ultimately delivered via the bloodstream to the parietal cells. The patented paste formulation of Gastrogard® (omeprazole) provides that protection, which unprotected powders and compounds do not have. With that said, there is still individual variability in the absorption of omeprazole, and the presence of food within the stomach may inhibit its bioavailability. Therefore, ideally, omeprazole should be given in the morning prior to feeding, followed by a 60-minute wait before feeding hay. Grain can be fed 30 to 60 minutes after hay feeding.[3] Injectable omeprazole is not available as an FDA-approved product in the United States, and the compounded products lack oversight as to safety, stability and concentration. Because omeprazole is a substituted benzimidazole, there has been interest in the potential value of the benzimidazole anthelmintic fenbendazole for treatment of gastric ulcer disease in the horse. At present, there is insufficient scientific evidence to support the use of fenbendazole or other benzimidazole compounds for the treatment of EGUS.

Histamine receptor antagonists have also been evaluated in horses. Cimetidine has little scientific evidence to show efficacy in the treatment of EGUS. Ranitidine (6.6 mg/kg PO q8h) has shown efficacy in improving ulcer scores in some horses when management changes were also made. However, omeprazole has been shown to be superior in healing and preventing gastric ulcers in training and racing horses.[4]

Antacids, including nutraceuticals, have not been determined to be effective in the treatment of EGUS. Antacids may act rapidly to neutralize acid, but do not have a long duration of activity, ranging from 15 to 90 minutes in the horse. Therefore, they must be administered frequently (up to six to 12 times/day), yet still do not suppress acid for long enough to allow ulcer healing. They can be used to ameliorate clinical signs, and as such, have been used to support the need to confirm a definitive diagnosis with gastroscopy.

OTHER PHARMACOLOGIC TREATMENTS

The reason for poor response of EGGD to monotherapy with omeprazole is not well understood; however, given the assumption that mucosal barrier defects play a role in the pathophysiology of EGGD, the use of mucosal protectants as a component of treatment is recommended. Therefore, acid suppression with omeprazole is often combined with sucralfate for treatment of EGGD.

Sucralfate, a complex sulfated polysaccharide salt of sucrose and aluminum hydroxide, has been used somewhat successfully to treat gastric and duodenal ulcers in humans. Its mechanism of action involves adherence to the ulcerated surface, forming a proteinaceous bandage and stimulating increased prostaglandin E1 synthesis and mucus secretion. It also inactivates pepsin and adsorbs bile acids. Sucralfate can be dosed at 12-40 mg/kg q 6–12h. While sucralfate alone does not result in ulcer healing, it is recommended to be used with omeprazole in the treatment of EGGD.[5] As evidence, the use of omeprazole at 4mg/kg PO once daily and sucralfate at 12mg/kg PO twice daily resulted in healing rates of 67.5% for EGGD of the pyloric antrum.[6] It is important to separate sucralfate administration from other oral drugs by at least 30 minutes, however, as it will affect their absorption.

Misoprostol is a synthetic prostaglandin analog that has also been used for EGGD, although with limited evidence. It has a cytoprotective effect from stimulation of bicarbonate and mucus secretion, increased mucosal blood flow, decreased vascular permeability, and increased cellular proliferation and migration. In one small study of 40 sport horses, misoprostol at 5 ug/kg PO BID resulted in healing in 73% of horses.[7] It is important to note that misoprostol is not licensed for use in horses, and has the potential to cause abortion in humans and potentially horses, so it should be handled with caution. Diarrhea and abdominal discomfort have also been reported.

Antimicrobials are not considered first-line treatment for either form of EGUS, as bacterial contribution to the pathophysiology of disease remains unclear. In cases of chronic non-responsive ulcers, where secondary bacterial infection of ulcers may be delaying healing, antibiotics or probiotics may be considered.

Duration of treatment for EGGD is more difficult to predict and generally longer. Endoscopic reexamination should be performed around 30 days of treatment to gauge response, need for change in treatment, or need for extension of current treatment.

PHARMACOLOGIC PREVENTION

Once ulcers have healed, omeprazole prophylaxis can be considered in horses still undergoing active training or other risk factors. It has been shown that omeprazole at 1.0 mg/kg will reduce the risk of gastric ulceration in training horses.[8]

MANAGEMENT STRATEGIES

Adjustments in management practices are also critical to the overall treatment outcomes. General management strategies for EGUS prevention include decreasing stress and adjusting nutritional management.

Decreasing stress means different things to different horses, but paying attention to social structure and exercise needs can help. As frequency of exercise > 6 days per week has been linked to EGGD,[9] providing more rest days may be of some benefit. Walking has been demonstrated to increase gastric contractility and outflow as well as colonic motility. Allowing as much turnout as possible may have both physical and behavioral benefits in these cases.

Nutritional changes can include both the content of feed as well as timing. The presence of roughage in the stomach physically limits acid contact with the squamous lining. It is important to point out to horse owners that any purposeful fasting prior to omeprazole administration is only to be during the treatment phase, as regular forage consumption is important in the management strategy to prevent recurrence. Acid secretion is increased by feeding grain concentrates to horses, as the feedstuff causes an increase in the release of intestinal gastrin. Decreasing starch may also decrease volatile fatty acid production, and therefore raise gastric pH. Therefore, offering horses free-choice hay and limiting grain feeding are important considerations. In addition, feeding hay, especially alfalfa, which provides additional buffering due to its calcium and phosphorus content, prior to grain meals and prior to exercise is recommended. Increasing bicarbonate-rich saliva production by feeding horses at ground level and feeding roughage will increase acid buffering. Addition of corn oil may also decrease gastric acid output.[10]

CONCLUSIONS

Treating EGUS in all forms remains important to the health and welfare of horses worldwide. Continued research is needed to further our understanding of where ESGD and EGGD overlap and where they diverge in terms of pathophysiology, treatment and prevention. In the meantime, practitioners should strive to use gastroscopy to localize and characterize the lesions, thus allowing pharmacologic and management strategies to be best tailored to the individual diagnosis.

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GASTROGARD®

(omeprazole) Oral Paste for Equine Ulcers

Oral Paste for Horses and Foals

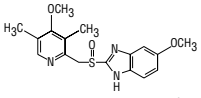
- Approved by FDA under NADA # 141-123

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] 1Hbenzimidazole. 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 F (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-aday for 4 weeks at the recommended dosage of 1.8 mg omeprazole/lb body weight (4 mg/kg). For the prevention of recurrence of gastric 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 weightmarking 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:**
  1) While holding plunger, turn the knurled ring on the plunger ¼ turn to the left and slide the knurled ring along the plunger shaft so that the side nearest the barrel is at the appropriate weight marking, aligning the arrows on the ring and plunger as shown in the pictogram.
  2) Lock the ring in place by making ¼ turn to the right.
  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.
- To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or online at www.fda.gov/reportanimalae.

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 cannaliculi 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).
- **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 (AUC0-∞). When comparing the individual bioavailability data (AUC0-∞ , Cmax, and Tmax 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 AUC0-∞ 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 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 the 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: inappetance 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), excessive 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.

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