

# News Release



## FOR IMMEDIATE RELEASE

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### **Appaloosa Horse Club Approves EQUIOXX<sup>®</sup> (firocoxib), ULCERGARD<sup>®</sup> (omeprazole) and GASTROGARD<sup>®</sup> (omeprazole) Organization offers FDA-approved options to members nationwide**

**DULUTH, GA — Nov. 12, 2008** — Starting Jan. 1, 2009, Appaloosa Horse Club (ApHC) members will be able to use EQUIOXX<sup>®</sup> (firocoxib), ULCERGARD<sup>®</sup> (omeprazole) or GASTROGARD<sup>®</sup> (omeprazole) prior to competition.<sup>1</sup>

The decision by the ApHC Board of Directors provides thousands of horse owners nationwide with FDA-approved options for common diseases like equine osteoarthritis and stomach ulcers.<sup>1</sup>

"I believe these products are great options to help us maintain the health of our equine partners," says Frank Larrabee, president of the ApHC Board of Directors. "Personally, my own horses have experienced stomach ulcers and the need for NSAIDs, and I'm sure the thousands of Appaloosa members involved in equine activities are faced with the same concerns. We salute the efforts of the researchers who have helped make life a little easier on these horses."

With the approval, EQUIOXX is the only nonsteroidal anti-inflammatory drug (NSAID) approved for use up to 14 consecutive days in the ApHC.<sup>1</sup> EQUIOXX also is approved for use in the American Quarter Horse Association<sup>2</sup> and United States Equestrian Federation.<sup>3</sup>

EQUIOXX is the first equine oral NSAID to be approved in more than 20 years. It is proven to control joint pain and inflammation associated with equine osteoarthritis, which is one of the most common causes of lameness in horses. Also known as degenerative joint

(more)

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disease, osteoarthritis can develop in horses as young as 2 years old.<sup>4</sup> EQUIOXX works quickly to provide 24 hours of pain relief and is easily administered as an oral paste.<sup>5</sup>

The ApHC also approved GASTROGARD and ULCERGARD for use no more than 24 hours prior to competition.<sup>1</sup> GASTROGARD and ULCERGARD are the first and only FDA-approved products for the treatment and prevention of equine stomach ulcers, respectively.

Horses can develop stomach ulcers in as little as five days,<sup>6</sup> but GASTROGARD can treat stomach ulcers even while horses continue to train. Proactive use of ULCERGARD during short or long periods of time\* can help reduce the risk of stomach ulcers in horses that regularly deal with stressful situations, such as training, traveling and competing.<sup>7</sup>

"Equine osteoarthritis and stomach ulcers are common for horses of all breeds," says Dr. Frank Hurtig, director, Veterinary Services, Merial. "Now, competitors in ApHC events can help ensure their horses have FDA-approved choices to help them address these diseases and enable their horses to compete at their best."

For complete ApHC rules regarding the use of EQUIOXX, GASTROGARD and ULCERGARD, please visit [www.appaloosa.com](http://www.appaloosa.com).

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 5,000 people and operates in more than 150 countries worldwide. Its 2007 sales were nearly \$2.5 billion. Merial Limited is a joint venture between Merck & Co., Inc. and sanofi-aventis. For more information, please see [www.merial.com](http://www.merial.com).

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*As with any prescription medication, prior to use, a veterinarian should perform a physical examination and review the horse's medical history. A veterinarian should advise horse owners to observe for signs of potential drug toxicity. As a class, nonsteroidal anti-inflammatory drugs may be associated with gastrointestinal and renal toxicity. Use with other NSAIDs, corticosteroids or nephrotoxic medication should be avoided. EQUIOXX has not been tested in horses less than 1 year of age or in breeding horses, or pregnant or lactating mares. For additional information please refer to the prescribing information or visit [www.equioxx.com](http://www.equioxx.com).*

*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](http://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*

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*evaluated. ULCERGARD may be used safely in breeding stallions. Safety in pregnant mares has not been determined.*

<sup>1</sup>When treated for 8 or 28 days, ULCERGARD is proven to effectively prevent stomach ulcers in horses exposed to stressful conditions.

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<sup>1</sup>Appaloosa Horse Club Board of Directors unapproved summary of motions. July 6, 2008. Available at: [http://www.appaloosa.com/pdfs/SummaryofMotions07\\_06\\_08.pdf](http://www.appaloosa.com/pdfs/SummaryofMotions07_06_08.pdf). Accessed August 20, 2008.

<sup>2</sup>American Quarter Horse Association. Show rules and regulations. *Official Handbook of Rules and Regulations*. 2008: 128. Available at: [http://www.aqha.com/association/registration/pdf/showrules\\_08.pdf](http://www.aqha.com/association/registration/pdf/showrules_08.pdf). Accessed February 1, 2008.

<sup>3</sup>United States Equestrian Federation. *Drugs and Medications Guidelines*. 2007: 2-3. Available at: <http://www.usef.org/documents/competitions/2007/2007DrugsMedsGuidelines.pdf>. Accessed February 13, 2008.

<sup>4</sup>Schlueter AE and Orth MW. Equine osteoarthritis: a brief review of the disease and its causes. *Equine and Comparative Exercise Physiology* 2004; 1(4): 221–231.

<sup>5</sup>EQUIOXX Freedom of Information Summary.

<sup>6</sup>McClure 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.

<sup>7</sup>ULCERGARD product label.

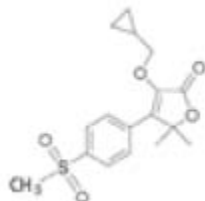
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Non-steroidal anti-inflammatory drug for oral use in horses only.

**CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.**

**Description:** EQUIOXX® (firocoxib) belongs to the coxib class of non-narcotic, non-steroidal anti-inflammatory drugs. Firocoxib is a white crystalline compound described chemically as 3-(cyclopropylmethoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethylfuranone. The empirical formula is C<sub>17</sub>H<sub>20</sub>O<sub>5</sub>S, and the molecular weight is 336.4. The structural formula is shown below:



**Indications:** EQUIOXX Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

**Dosage and Administration:** Always provide the Client Information Sheet with the prescription. The recommended dosage of EQUIOXX (firocoxib) for oral administration in horses is 0.045 mg/lb (0.1 mg/kg) of body weight once daily for up to 14 days. In target animal safety studies, toxicity was seen at the recommended dose when the duration of treatment exceeded 30 days.

Each marking on the syringe will treat 250 pounds of body weight, and each notch corresponds to approximately a 50 lb weight increment. To deliver the correct dose, round the horse's body weight up to the nearest 50 lb increment (if the body weight is an exact 50-lb increment, do not round up). Unlock the knurled ring on the syringe plunger by rotating it ¼ turn. Slide the knurled ring along the plunger shaft so that the side nearest the barrel is at the appropriate 50 lb weight notch. Rotate the plunger ring ¼ turn to lock it in place and ensure it is locked.

EQUIOXX may be given with or without food.

**Contraindications:** Horses with hypersensitivity to firocoxib or other NSAIDs should not receive EQUIOXX Oral Paste.

**Warnings: For oral use in horses only. Do not use in horses intended for human consumption.**

Human Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

Animal Safety: Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. For technical assistance or to report suspected adverse events, call 1-877-217-3543.

**Precautions:** Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. See **Information for Owner or Person Treating Horse** section of this package insert.

Treatment with EQUIOXX should be terminated if signs such as inappetence, colic, abnormal feces, or lethargy are observed.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal and gastrointestinal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been

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previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The concomitant use of protein bound drugs with EQUIOXX Oral Paste has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of EQUIOXX Oral Paste has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of EQUIOXX Oral Paste in horses less than one year in age, horses used for breeding, or in pregnant or lactating mares has not been evaluated.

Consider appropriate washout times when switching from one NSAID to another NSAID or corticosteroid.

**Adverse Reactions:** In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given EQUIOXX Oral Paste at a dose of 0.045 mg/lb (0.1 mg/kg) orally once daily for up to 14 days. The following adverse reactions were observed. Horses may have experienced more than one of the observed adverse reactions during the study.

**Adverse Reactions Seen in U.S. Field Studies**

Adverse Reactions	EQUIOXX n=127	Active Control n=125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose stool	1	0
Polydipsia	0	1
Urticaria	0	1

EQUIOXX (firocoxib) Oral Paste was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics, during the field studies.

**Information for Owner or Person Treating Horse:** You should give a Client Information Sheet to the person treating the horse and advise them of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include erosions and ulcers of the gums, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in rare situations, result in death.

Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any of these signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

### **Clinical Pharmacokinetics/Pharmacodynamics:**

**Pharmacokinetics:** When administered as a 0.045 mg/lb (0.1 mg/kg) dose in oral paste to adult horses with normal access to roughage, feed, and water, the absolute bioavailability of firocoxib from EQUIOXX paste is approximately 79%. Following oral administration, drug peak concentration (C<sub>max</sub>) of 0.08 mcg/mL can be reached at 4 hours (T<sub>max</sub>) post-dosing. However, in some animals, up to 12 hours may be needed before significant plasma concentrations are observed. Little drug amount distributes into blood cells. The major metabolism mechanism of firocoxib in the horse is decyclopropylmethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of label is eliminated in the urine as the decyclopropylmethylated metabolite. Despite a high rate of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean V<sub>d(ss)</sub> = 1652 mL/kg). The terminal elimination half-life (T<sub>1/2</sub>) in plasma averages 30-40 hours after IV or oral paste dosing. Therefore, drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 6-8 daily oral doses in the horse. Dose linearity exists from 1X-2X of 0.1 mg/kg/day.

**Mode of Action:** EQUIOXX (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity in animal models.

**Effectiveness:** Two hundred fifty-three client-owned horses of various breeds, ranging in age from 2 to 37 years and weighing from 595 to 1638 lbs, were randomly administered EQUIOXX or an active control drug in multi-center field studies. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Horses were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall clinical improvement in a non-inferiority evaluation of EQUIOXX compared to an active control. At study's end, 84.4% of horses treated with EQUIOXX were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with EQUIOXX showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

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**Acceptability:** EQUIOXX Oral Paste was rated both convenient to administer (95.3%) and acceptable to the horse (97.6%) by owners in the multi-center field study.

**Animal Safety:** In a target animal safety study, firocoxib was administered orally to healthy adult horses (two male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3, and 5X the recommended dose) for 30 days. Administration of firocoxib at 0.3 and 0.5 mg/kg body weight was associated with an increased incidence of oral ulcers as compared to the control group but, no oral ulcers were noted with 0.1 mg/kg. There were no other drug-related adverse findings in this study.

In another target animal study, firocoxib was administered orally to healthy adult horses (four males or male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 42 days. Administration of firocoxib at 0.1, 0.3 and 0.5 mg/kg body weight was associated with delayed healing of pre-existing oral (lip, tongue, gingival) ulcers. In addition, the incidence of oral ulcers was higher in all treated groups as compared to the control group.

Clinical chemistry and coagulation abnormalities were seen in several horses in the 0.5 mg/kg (5X) group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study, prolonged buccal mucosal bleeding time (BMBT), and a dilated pelvis of the right kidney. Another 5X male had a similar mild increase in creatinine during the study but did not have any gross abnormal findings. One female in the 5X group had a prolonged BMBT, bilateral tubulointerstitial nephropathy and bilateral papillary necrosis.

Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse discussed above with the prolonged BMBT. Papillary necrosis was present in one 1X male horse and the 5X female horse discussed above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (three females, two male castrates and one male per group) at 0, 0.25 mg/kg, 0.75 mg/kg and 1.25 mg/kg (2.5, 7.5 and 12.5X the recommended dose of 0.1 mg/kg) for 92 days. An additional group of three females, two male castrates and one male per group, was dosed at 1.25 mg/kg for 92 days but was monitored until Days 147-149. There were treatment-related adverse events in all treated groups. These consisted of ulcers of the lips, gingiva and tongue and erosions of the skin of the mandible and head. Gross and microscopic lesions of the kidneys consistent with tubulointerstitial nephropathy were seen in all treated groups. Papillary necrosis was seen in the 2.5X and the 12.5X groups. In addition, several 12.5X horses had elevated liver enzymes (GGT, SDH, AST and ALT). One 2.5X horse had increased urine GGT and urine protein levels which was due to renal hemorrhage and nephropathy. Gastric ulcers of the margo plicatus and glandular area were more prevalent in the 2.5X and 7.5X groups, but not seen in the 12.5X group. The group of horses that were monitored until Days 147-149 showed partial to full recovery from oral and skin ulcers, but no recovery from tubulointerstitial nephropathy.

**Storage Information:** Store below 86°F (30°C). Brief excursions up to 104°F (40°C) are permitted.

**How Supplied:** EQUIOXX is available in packs of 20, 72 and 216 individually-boxed syringes. Each syringe contains 6.93 grams of EQUIOXX paste, sufficient to treat a 1250 lb. horse

For technical assistance or to report suspected adverse reactions, call 1-877-217-3543.  
NADA 141-253, Approved by FDA

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U.S. Pat. No.: 5981576, 6020343

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1050-2012-01 Rev. 02-06

# ApHC Approves EQUIOXX, GASTROGARD, ULCERGARD Nov. 12, 2008



**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.

## **Indications**

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

## **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<sup>+</sup>, K<sup>+</sup> AT Pase 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<sup>+</sup>, K<sup>+</sup> AT Pase activity/turnover. Once all of the enzyme becomes bound, acid secretion resumes only after new H<sup>+</sup>, K<sup>+</sup> AT Pase 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 (AUC<sub>0-</sub>). When comparing the individual bioavailability data (AUC<sub>0-</sub>, C<sub>max</sub>, and T<sub>max</sub> 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<sub>0-</sub> 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*<sup>®</sup> (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 (4mg/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: 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), 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 and please visit our Web site at [www.gastrogard.com](http://www.gastrogard.com). Marketed by: Merial Limited, Duluth, GA 30096-4640 (Merial Limited: Registered in England and Wales (Reg.N.3332751) with registered offices at 27 Knightsbridge, London, SW1X 7QT, England and domesticated in Delaware, USA as Merial LLC). US Patent 4255431 and 5708017 Copyright ©2001 Merial Limited. All rights reserved. May 2001