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USEF Approves Use of EQUIOXX[®] (firocoxib) New option for equine osteoarthritis pain relief

DULUTH, GA. — Oct. 18, 2007 — Recently, the United States Equestrian Federation (USEF) established use guidelines for EQUIOXX[®] (firocoxib), the first orally administered equine nonsteroidal anti-inflammatory drug (NSAID) to be approved by the FDA in 20 years. The new rule lists firocoxib as an NSAID and allows a maximum permitted concentration in a horse's blood plasma that follows the product label recommendations for using EQUIOXX. The USEF ruling took effect on Aug. 1, 2007.

"This ruling is important because it provides horse owners competing in USEF events with another option for treating pain and inflammation associated with osteoarthritis," said Peter Hanson, DVM, PhD, Dipl ACVS, executive director, pharmaceutical R&D projects, Merial. "In addition to rapid and sustained relief from osteoarthritis, the safety profile of EQUIOXX allows use for up to 14 consecutive days surrounding a USEF event."

Osteoarthritis is known to affect horses of all ages, even very young ones.¹ The onset of the disease is commonly due to one or more of the following factors: trauma to the joint, conformation faults, immobilization, improper shoeing and age. Training, racing and performing all accelerate the possibility of a horse's joints being damaged.¹

To help relieve the pain and inflammation associated with equine osteoarthritis, EQUIOXX is quickly absorbed.² In addition, EQUIOXX lasts 24 hours for less frequent dosing. One study showed that after one dose of EQUIOXX, firocoxib was maintained at adequate blood levels to ensure effectiveness until the next dose 24 hours later.³

The official USEF statement regarding the use of EQUIOXX states:

(more)

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“The Board of Directors for the United States Equestrian Federation has approved the use of the new Non-Steroidal Anti-Inflammatory Drug (NSAID) EQUIOXX® (firocoxib). This new NSAID is the first highly COX-1 sparing* drug to be FDA approved for use in horses.

“The rule allowing the use of firocoxib will take effect on 8/1/07. Until this time, the use of firocoxib is restricted to use outside competition.

“The new rule lists firocoxib as an NSAID with a restrictive quantitative limit, and allows for a maximum permitted concentration of 0.240 micrograms per milliliter of blood plasma. The recommendation for appropriate dose and time consideration is to follow the manufacturer’s guidelines for its use at 0.1 milligram per kilogram of body weight once daily. This corresponds with a 45.5 milligram dose for a 1000 lb. horse, and should be given no sooner than 12 hours prior to competing. Firocoxib is permitted to be used for a period of 14 consecutive days. Until further review by the Fédération Equestre Internationale (FEI), per manufacturer recommendation, firocoxib should not be used in a horse in the 30 days prior to competing in an FEI sanctioned event.”

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 2006 sales were nearly \$2.2 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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As with any prescription medication, prior to use, your veterinarian should perform a physical examination and review your horse’s medical history. Your veterinarian will advise you 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.

*Clinical relevance has not been determined.

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¹Schlueter AE and Orth MW. Equine osteoarthritis: a brief overview of the disease and its causes. *Equine and Comparative Exercise Physiology* 2004; 1 (4): 221-231.

²Data on file at Merial, “Clinical Experience Report, PHN 471, Target Animal Safety Evaluation, Firocoxib (ML-1,785,713) Oral Paste for Horses.”

³Data on file at Merial, Pharmacokinetic Study, PR&D 0096601.

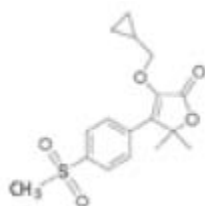
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Non-steroidal anti-inflammatory drug for oral use in horses only.

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 C₁₇H₂₀O₅S, 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

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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 inappetance, 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 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 on 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.

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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_{max}) of 0.08 mcg/mL can be reached at 4 hours (T_{max}) 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_{d(ss)} = 1652 mL/kg). The terminal elimination half-life (T_{1/2}) 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.

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

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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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