NSAIDs – Are You Following the Rules?

As equestrians, we expect a lot from our performance horses. Sometimes pain and inflammation of their joints can happen right before a show or competition. Before administering a non-steroidal anti-inflammatory drug (NSAID), it's important to know the rules specific to your particular association or show.

NSAIDs are typically used to treat conditions such as the pain and inflammation associated with equine osteoarthritis.[1] Most shows follow the United States Equestrian Federation (USEF) Equine Drugs and Medications Rule, which outlines specifics in regard to NSAIDs. There are seven Food and Drug Administration (FDA)-approved NSAIDs approved for use by the USEF, as well as the American Quarter Horse Association (AQHA): diclofenac liposomal cream, firocoxib, phenylbutazone, flunixin meglumine, ketoprofen, meclofenamic acid and naproxen.[2,3]

Here are some basics to know before treating your horse with an NSAID prior to competition:

- NSAIDs are to be administered to a horse or pony only for a therapeutic purpose.[2]
- There are specific administration guidelines for each NSAID that must be followed,[2] which can be found on the USEF website.
- Only one NSAID (of those permitted to be used) may be used at a time.[2]
- Whenever a permitted NSAID is administered, any additional permitted NSAID should not have been administered during the three days prior to competing.[2]
- NSAIDs that don't appear on the permitted list must not be administered during the seven days prior to competing.[2]
- The dose should be accurately calculated according to the actual weight of the animal.[2]
- The latest an NSAID can be given is 12 hours prior to competition.[2]

Many competitors choose EQUIOXX® (firocoxib) because it provides 24 hours of prescription equine osteoarthritis pain relief* in just one daily dose.[4] There are two formulations available: injection and paste. The overall duration of treatment with EQUIOXX Injection and EQUIOXX Oral Paste will be dependent on the response observed, but should not exceed 14 days.[2] Other oral NSAIDs are approved for only five consecutive days.[2]

In addition to giving the correct remedy, it's important to give the correct dose. Hoyt Cheramie, DVM, MS, manager, Merial Large Animal Veterinary Services, said there are

potential dangers when administering an NSAID.

"Most NSAIDs are administered with a notched syringe, with one dose being just a small portion of the entire tube," Cheramie says. "It is not unheard of for a horse owner to unknowingly give an overdose of an NSAID, which can lead to health complications such as gastric ulcers, diarrhea, anorexia and renal dysfunction."[5]

Cheramie also recommends using a product that can be administered just once a day versus multiple times so owners don't have to worry about inadvertently exposing their horse to peaks and valleys in relief.[6]

"When a horse needs relief from discomfort at home or at a show, owners should partner with their veterinarians to determine the best treatment option and be diligent about following dosing directions," Cheramie says. He noted that when it comes to giving medications, horse owners, trainers and veterinarians should read the rules specific to each association or show, ensuring they are in compliance.

*Joint pain and inflammation associated with equine osteoarthritis, also called degenerative joint disease.

IMPORTANT SAFETY INFORMATION
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, hepatic 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.

[1] United States Equestrian Federation. NSAIDs and Your Horse. Available at: http://issuu.com/equestrian/docs/nsaidandyourhorseweb?mode=embed&layout=http. Accessed July 16, 2015.
[2] United States Equestrian Federation. *Drugs and Medications Guidelines*. 2014:2-3. Available at: https://www.usef.org/documents/drugsMeds/2015/drugsmedsguidelines15_web.pdf. Accessed July 16, 2015.
[3] AQHA *Official Handbook of Rules and Regulation*. 2015:22: VIO405.7. Available at: http://aqha.com/~/media/Files/Resources/Handbook/2015%20Handbook-%20Shows.ashx. Accessed July 16, 2015.
[4] EQUIOXX product label.
[5] Reed SK, Messer NT, Tesman RK, Keegan KG. Effects of phenylbutazone alone or in

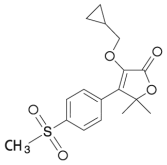
combination with flunixin meglumine on blood protein concentrations in horses. *Am J Vet Res*. 2006;67(3)398-402.
[6] The United States Pharmacopeial convention. Phenylbutazone. 2004. Available at: http://c.ymcdn.com/sites/www.aavpt.org/resource/resmgr/imported/phenylbutazone.pdf. Accessed July 16, 2015.

Equioxx® Injection (firocoxib)

Non-steroidal anti-inflammatory drug for intravenous 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 (NSAID). Firocoxib is a white crystalline compound described chemically as 3-(cyclopropylmethoxy)-4-(4-(methylsulfo nyl)phenyl)-5, 5-dimethylfuranone. The empirical formula is $C_{17}H_{20}O_5S$, and the molecular weight is 336.4. The structural formula is shown below:



EQUIOXX Injection is a colorless to pale yellow solution. Each mL of EQUIOXX Injection for Horses contains 20 mg of firocoxib as a free base, 550 mg of polyethylene glycol (PEG 400) and 600 mg of glycerol formal.

Indications: EQUIOXX Injection is administered for up to 5 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 Injection for intravenous administration in horses is 0.04 mg/lb (0.09 mg/kg) of body weight once daily for up to 5 days. If further treatment is needed, EQUIOXX (firocoxib) Oral Paste for horses can be used at a dosage of 0.045 mg/lb (0.1 mg/kg) body weight for up to an additional 9 days of treatment. The overall duration of treatment with EQUIOXX Injection and EQUIOXX Oral Paste will be dependent on the response observed, but should not exceed 14 days. See EQUIOXX Oral Paste for horses package insert for dosage and administration. EQUIOXX Injection is a non-aqueous solution and should not be mixed with aqueous solutions (Do not flush through intravenous lines using aqueous flush solutions).

Contraindications: Horses with hypersensitivity to firocoxib should not receive EQUIOXX Injection.

Warnings: For intravenous 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 human exposure.

Animal Safety: Clients should be advised to observe for signs of potential drug toxicity and be give 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 inappetance, colic, abnormal feces, or lethargy are observed.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Horses that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. 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 and/or gastrointestinal perforation, concomitant use of EQUIOXX Injection with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided.

The concomitant use of protein bound drugs with EQUIOXX Injection for horses has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of firocoxib Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

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

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

Adverse Reactions: The effectiveness of EQUIOXX Injection was established in a biocomparability study demonstrating that EQUIOXX Oral Paste is bioequivalent to EQUIOXX Injection. Thus, additional field studies were not performed to support the effectiveness of EQUIOXX Injection.

In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given EQUIOXX® (firocoxib) Oral Paste for Horses 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.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet, please call 1-877-217-3543.

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 some 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.

Adverse Reactions Seen in U.S. Field Studies with EQUIOXX Oral Paste

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

Clinical Pharmacokinetics/ Pharmacodynamics: Based on the comparison data between the intravenous and oral administration, the area under the curve (AUC) for both routes of administration was the same. The average AUC ratio of injectable to the oral product was 103%. The average peak plasma concentration observed one minute following firocoxib intravenous administration was approximately 3.7 fold greater than the observed average peak plasma concentration reached after administration of the oral paste (oral T_{max} = 2.02 hours). The average plasma concentrations following IV injection and oral administration were similar by 2 hours post-dose, after which the concentrations proceeded to decline in parallel. The terminal elimination half-life (T ½ el) values were not significantly different (p>0.05), with values ranging from 14.6 to 68.0 hrs (mean = 31.5 hours) for the oral paste and from 12.6 to 66.3 (mean = 33.0 hours) for the intravenous solution.

The major metabolism mechanism of firocoxib in the horse is decyclopropylmethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of firocoxib is eliminated in the urine as the glucuronide conjugate of the decyclopropylmethylated metabolite. Despite a high rate of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean Vd (ss) = 1652 mL/kg). The 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 after oral administration. Little drug amount distributes into blood cells.

Steady-state plasma firocoxib concentrations at 4 and 24 hours post administration were the same following intravenous or oral administration at each dose in the range of 1X to 5X.

Mode of action: Firocoxib is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity[1] in animal models. Based on *in vitro* horse data, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of the inducible cyclooxygenase-2 isoenzyme (COX-2)[2,3]. Firocoxib selectivity for the constitutive isoenzyme, cyclooxygenase-1 (COX-1), is relatively low. However, the clinical significance of these in vitro selectivity findings has not been established.

Effectiveness: The effectiveness of EQUIOXX Injection was established in a biocomparability study evaluating EQUIOXX Oral Paste and EQUIOXX Injection. Thus, additional field studies were not performed to support the effectiveness of EQUIOXX Injection. 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 Oral Paste 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 Oral Paste compared to an active control.

At study's end, 84.4% of horses treated with EQUIOXX Oral Paste were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with EQUIOXX Oral Paste showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

Animal Safety: A target animal safety study was conducted to assess the safety of EQUIOXX Injection followed by EQUIOXX Oral Paste in the horse. Thirty-two clinically healthy adult horses received EQUIOXX Injection intravenously once daily for five days at doses of either 0 mg/kg (control group); 0.09 mg/kg (1X); 0.27 mg/kg (3X); or 0.45 mg/kg (5X the recommended dose). This was followed by once daily oral administration of EQUIOXX Oral paste for nine days at doses of either 0 mg/kg (control group); 0.1 mg/kg (1X); 0.3 mg/kg (3X); or 0.5 mg/kg (5X the recommended dose). This sequence (five days of EQUIOXX Injection followed by nine days EQUIOXX Oral Paste, for a total of 14 days) was repeated three times for a total treatment duration of 42 days (3X the recommended treatment duration of 14 days).

Two male 5X horses demonstrated a white focus in the renal cortex which correlated with tubulointerstitial nephropathy microscopically. The presence of tubulointerstitial nephropathy was considered treatment-related.

One horse from the control group and two horses from the 5X group had injection site swellings during treatment. Injection site changes characterized by inflammatory cell influx and rarely tissue necrosis were seen in all study groups including the control group.

There was a dose-dependent increase in the incidence of oral ulcers and erosions. Elevated hepatic enzymes (GGT or AST) were noted in all study groups at one or more timepoints. One male 5X horse with an elevated GGT value on Day 42 was noted to have tubulointerstitial nephropathy at the time of necropsy. For all horses, these hepatic enzyme elevations generally returned to the reference range by the next time point.

Storage: Store at 20-25°C with excursions between 15-30°C.

How Supplied: EQUIOXX (firocoxib) Injection for Horses will be supplied in sterile, 25 mL amber glass vials for multi-dose use.

[1] McCann ME, Rickes EL, Hora DF, Cunningham PK et al. *In vitro* effects and *In vivo* efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res. 2005 Jul;66 (7):1278-84

[2] McCann ME, Anderson DR, Brideau C et al. *In vitro* activity and *in vivo* efficacy of a novel COX-2 inhibitor in the horse. Proceedings of the Academy of Veterinary Internal Medicine. 2002. Abstract 114, p.789.

[3] Data on file.

Manufactured for:
Merial Limited
Duluth, GA 30096-4640, U.S.A.
1-877-217-3543

Made in Germany

NADA 141-313, Approved by FDA

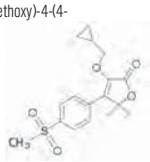
Rev. 12-2011

Equioxx® (firocoxib)

Oral Paste for Horses (firocoxib)
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 $C_{17}H_{20}O_5S$, 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 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.

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.

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.

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 (Cmax) of 0.08 mcg/mL can be reached at 4 hours (Tmax) 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 Vd(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[1] in animal models.

Based on *in vitro* horse date, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of inducible cyclooxygenase-2-isoenzyme (COX-2)[2,3]. Firocoxib selectivity for the constitutive isoenzyme, cyclooxygenase-1 (COX-1) is relatively low. However, the clinical significance of these *in vitro* selectivity findings has not been established.

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 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.

[1]McCann ME, Rickes EL, Hora DF, Cunningham PK et al. *In vitro* effects and *in vivo* efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res. 2005 Jul;66 (7): 1278-84
[2]McCann ME, Anderson DR, Brideau C et al. *In vitro* activity and *in vivo* efficacy of a novel COX-2 inhibitor in the horse. Proceedings of the Academy of Veterinary Internal Medicine. 2002 Abstract 114, p.789.
[3]Data on file.

Marketed by: Merial LLC, Duluth, GA 30096-4640
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For technical assistance or to report suspected adverse reactions, call 1-877-217-3543.
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