

Two Different Treatments to Reduce Inflammation

Healthy, normal functioning joints are essential in performance horses. Beyond the temporary effects of interfering with training and competition schedules, joint pain and inflammation lead to poor performance. Left untreated, inflammation from synovitis can worsen and lead to permanent cartilage degradation and other irreversible joint damage associated with osteoarthritis (OA).

Joint inflammation happens in all equine performance disciplines. The daily activities of horses in training can lead to everyday wear and tear on the joint, which results in synovial membrane and joint capsule inflammation (synovitis and capsulitis). In most cases of equine OA, it's this stress on the joint that initiates the process.

The healthy cartilage functions much like a sponge, absorbing synovial fluid during joint movement. As a result of inflammation, the articular cartilage becomes dehydrated. This creates more damage, which creates more inflammation in a self-perpetuating cycle. Following repeated bouts of inflammation, there is eventually loss of cartilage and permanent bony changes (OA).

Common signs associated with OA are stiffness and lameness, which are familiar words in the world of equine sports medicine.¹ If your horse shows these signs, consider speaking to your veterinarian about using LEGEND® (hyaluronate sodium) or EQUIOXX® (firocoxib) to control joint inflammation.

LEGEND is proven to safely and effectively treat non-infectious synovitis associated with equine OA.² It reduces joint inflammation as well as clinical and subclinical synovitis.

Many competitors choose a non-steroidal anti-inflammatory drug (NSAID) such as EQUIOXX because it provides relief of equine inflammation in just one daily dose.³ For competitions, EQUIOXX is the only NSAID approved for use up to 14 consecutive days by both the American Quarter Horse Association (AQHA) and the United States Equestrian Federation (USEF).^{4,5} BANAMINE® (flunixin meglumine) and Phenylbutazone can be used for no more than five consecutive days in AQHA and USEF competitions.^{4,5}

About Merial

Merial is a world-leading, innovation-driven animal health company, providing a comprehensive range of products that focus on disease prevention and overall health and wellness in animals. Merial has three main business areas: pets, farm animals, and veterinary public health, and our health solutions target more than 200 diseases and conditions across a variety of species. Merial employs 6,900 people and operates in more than 150 countries worldwide with over €2.5 billion of sales in 2015. Merial is a Sanofi company. For more information, please see www.merial.com; [@Merial](https://twitter.com/Merial).

IMPORTANT SAFETY INFORMATION:

LEGEND: The safety of LEGEND has not been evaluated in breeding stallions or in breeding, pregnant or lactating mares. The following adverse reactions have been reported following use of LEGEND Injectable Solution: Following intravenous use: occasional depression, lethargy, and fever. Following intra-articular (LEGEND Injectable Solution – 2 mL only) use: lameness, joint effusion, joint or injection site swelling, and joint pain.

EQUIOXX: 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.equiox.com.

®LEGEND and ®EQUIOXX are registered trademarks of Merial. All other marks are the properties of their respective owners. ©2016 Merial, Inc., Duluth, GA. All rights reserved. EQUILGN1626 (06/16)

¹Carmona JU, Prades M. Pathophysiology of Osteoarthritis. *Compendium Equine*. 2009;4:28- 40.

²LEGEND product label.

³EQUIOXX product label.

⁴AQHA Official Handbook of Rules and Regulation. 2016:VIO405. Available at: <https://www.aqha.com/media/9467/aqha-handbook-2016.pdf>. Accessed Feb. 22, 2016.

⁵United States Equestrian Federation. *Drugs and Medications Guidelines*. 2015:8-9. Available at: https://www.usef.org/documents/drugsMeds/2015/drugsmedsguidelines15_web.pdf. Accessed July 16, 2015.



LEGEND® Multi Dose (hyaluronate sodium)

For Intravenous Use in Horses Only
Not for Intra-Articular Use
and

LEGEND® (hyaluronate sodium) Injectable Solution

4 mL For Intravenous Use In Horses Only

2 mL For Intravenous or Intra-Articular Use In Horses Only

CAUTION:

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

DESCRIPTION:

LEGEND® (hyaluronate sodium) Injectable Solution and LEGEND® Multi Dose (hyaluronate sodium) Injectable Solution is a clear, colorless solution of low viscosity. LEGEND Injectable Solution is pyrogen free, sterile and does not contain a preservative. LEGEND Injectable Solution 2 mL is administered by intravenous or intra-articular injection. LEGEND 4 mL is for intravenous use only. LEGEND Multi Dose Injectable Solution is pyrogen free and sterile. It is administered by intravenous injection only.

Hyaluronic acid, the conjugate acid of hyaluronate sodium, is extracted from the capsule of *Streptococcus* spp. and purified, resulting in a form which is essentially free of protein and nucleic acids.

LEGEND Injectable Solution is supplied in 2 mL (20 mg) and 4 mL (40mg) vials. Each mL contains 10 mg hyaluronate sodium, 8.5 mg sodium chloride, 0.223 mg sodium phosphate dibasic, and 0.04 mg sodium phosphate monobasic. The pH is adjusted to between 6.5 and 8.0 with sodium hydroxide or hydrochloric acid.

LEGEND Multi Dose Injectable Solution is supplied in 20 mL vials. Each mL contains 10 mg hyaluronate sodium, 8.5 mg sodium chloride, 0.223 mg sodium phosphate dibasic, 0.04 mg sodium phosphate monobasic and 15.63 mg benzyl alcohol as a preservative. The pH is adjusted to between 6.5 and 8.0 with sodium hydroxide or hydrochloric acid.

CHEMISTRY:

Hyaluronic acid, a glycosaminoglycan, can exist in the following forms depending upon the chemical environment in which it is found: as the acid, hyaluronic acid; as the sodium salt, sodium hyaluronate (hyaluronate sodium); or as the hyaluronate anion. These terms may be used interchangeably but in all cases, reference is made to the glycosaminoglycan composed of repeating subunits of D-glucuronic acid and N-acetyl-D-glucosamine linked together by glycosidic bonds. Since this product originates from a microbial source, there is no potential for contamination with dermatan or chondroitin sulfate or any other glycosaminoglycan.

CLINICAL PHARMACOLOGY:

Hyaluronic acid is a naturally occurring substance present in connective tissue, skin, vitreous humour and the umbilical cord in all mammals. High concentrations of hyaluronic acid are also found in the synovial fluid. It also constitutes the major component of the capsule of certain microorganisms. The hyaluronic acid produced by bacteria is of the same structure and configuration as that found in mammals.

The actual mechanism of action for hyaluronate sodium in the healing of degenerative joint disease is not completely understood. One major function appears to be the regulation of normal cellular constituents. This effect decreases the impact of exudation, enzyme release and subsequent degradation of joint integrity. Additionally, hyaluronate sodium exerts an anti-inflammatory action by inhibiting the movement of granulocytes and macrophages.¹

Hyaluronate molecules are long chains which form a filter network interspersed with normal cellular fluids. It is widely accepted that injection directly into the joint pouch enhances the healing of inflamed synovium by restoring lubrication of the joint fluid. This further supplements the visco-elastic properties of normal joint fluid.

INDICATIONS:

LEGEND Injectable Solution and LEGEND Multi Dose Injectable Solution is indicated in the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis.

DOSE AND ADMINISTRATION:

LEGEND Multi Dose Injectable Solution:

4mL injected intravenously. Treatment may be repeated at weekly intervals for a total of three treatments.

Use aseptic technique and inject slowly into the jugular vein.

Horses should be given stall rest after treatment before gradually resuming normal activity.

LEGEND Injectable Solution 4mL:

4mL injected intravenously. Treatment may be repeated at weekly intervals for a total of three treatments.

Use aseptic technique and inject slowly into the jugular vein.

Horses should be given stall rest after treatment before gradually resuming normal activity.

Discard any unused portion of the drug and empty vial after opening.

LEGEND Injectable Solution 2mL:

Intravenously-4mL, Intra-articular-2mL in the carpus or fetlock. Treatment may be repeated at weekly intervals for a total of three treatments.

Strict aseptic technique should be observed when administering by intra-articular injection. As with any intra-articular procedure, proper injection site disinfection and animal restraint are important.

Excess joint fluid should be aseptically removed prior to injection. Care should be taken to avoid scratching the cartilage surface with the tip of the injection needle. Diffuse swelling lasting 24 to 48 hours may result from movement of the needle while in the joint space.

For intravenous administration, use aseptic technique and inject slowly into the jugular vein.

Horses should be given stall rest after treatment before gradually resuming normal activity.

Discard any unused portion of the drug and empty vial after opening.

CONTRAINDICATIONS:

There are no known contraindications for the use of LEGEND Solution and LEGEND Multi Dose Injectable Solution in horses.

RESIDUE WARNING:

Do not use in horses intended for human consumption.

HUMAN WARNINGS:

Not for use in humans. Keep this and all other drugs out of reach of children.

ANIMAL SAFETY WARNING:

For 4 mL only – Not for Intra-articular use.

Multi Dose not for Intra-articular use. The Intra-articular safety of hyaluronate sodium with benzyl alcohol has not been evaluated.

PRECAUTIONS:

Radiographic evaluation should be carried out in cases of acute lameness to ensure that the joint is free from serious fractures. As with any intra-articular (LEGEND Injectable Solution – 2 mL only) treatment, special precautions must be followed as to injection technique and sterility for prevention of possible swelling or infection. Intra-articular injections should not be made through skin that has been recently fired or blistered, or that has excessive scurf and counterirritant on it.

The safety of LEGEND Injectable Solution and LEGEND Multi Dose Injectable Solution has not been evaluated in breeding stallions or in breeding, pregnant or lactating mares.

ADVERSE REACTIONS:

No local or systemic side effects were observed in the LEGEND Injectable Solution clinical field trials with either intravenous or intra-articular injections.

Post-Approval Experience: While all adverse reactions are not reported, the following adverse reactions are based on voluntary post-approval reporting for LEGEND Injectable Solution:

Following **Intravenous** use: Occasional depression, lethargy, and fever.

Following **Intra-articular** (LEGEND Injectable Solution – 2 mL only) use: lameness, joint effusion, joint or injection site swelling, and joint pain.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Meril 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 <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation>.

EFFECTIVENESS:

Effectiveness studies utilizing LEGEND Multi Dose Injectable Solution were not performed. LEGEND Multi Dose Injectable Solution was approved based on the conclusion that the effectiveness of LEGEND Multi Dose Injectable Solution will not differ from that demonstrated for the original formulation of LEGEND Injectable Solution.

Forty-six horses with lameness in either the carpal or fetlock joints were treated intravenously or intra-articularly with LEGEND Injectable Solution in a well-controlled clinical study conducted at four locations. One, two or three injections were given based on clinical improvement. Overall clinical improvement was judged as excellent or good in 90% of the cases treated intravenously and 96% of those treated intra-articularly with LEGEND Injectable Solution.

ANIMAL SAFETY:

LEGEND Injectable Solution was administered to normal horses at one, three and five times the recommended intra-articular dosage of 20 mg and the intravenous dosage of 40 mg. Treatments were given once weekly for nine consecutive weeks (three times the maximum duration). No systemic clinical signs were observed nor were there any adverse effects upon hematology or clinical chemistry parameters. A transient, slight to mild post-injection swelling of the joint capsule occurred in some of the animals treated intra-articularly with LEGEND Injectable Solution – 2 mL as it did in the saline treated control horses. No gross or histological lesions were observed in the soft tissues or the surface areas of the treated joint.

Animal safety studies utilizing LEGEND Multi Dose Injectable Solution were not performed. LEGEND Multi Dose Injectable Solution was approved based on the conclusion that the safety of LEGEND Multi Dose Injectable Solution will not differ from that demonstrated for the original formulation of LEGEND Injectable Solution.

STORAGE:

Store at or below 77° F (25° C). Brief excursions to 104° F (40° C) are permitted.

For LEGEND Multi Dose Injectable Solution, discard remaining product 6 months after first use.

HOW SUPPLIED:

LEGEND Injectable Solution is supplied in a carton of six 2 mL (20 mg) bottles.

LEGEND Injectable Solution is supplied in a carton of six 4 mL (40 mg) bottles.

LEGEND Multi Dose Injectable Solution is supplied in 20 mL bottles.

NADA 140-883, Approved by FDA

Manufactured for: Meril, Inc., Duluth, GA 30096-4640, U.S.A.

REFERENCE:

¹Swanstorm OG. Hyaluronate (hyaluronic acid) and its use, Proc. American Assoc. Equine Pract., 24th annual convention. 1978;345-348.

To obtain product information, including a Material Safety Data Sheet, call 1-888-637-4251.

LEGEND Multi Dose Injectable Solution 08904327, 08904793, R. 1
September, 2010

LEGEND Injectable Solution 2 mL – 08710980-017599, 08715516-79001750, R. 12
September, 2010

LEGEND Injectable Solution 4 mL – 08710999-017699, 08715524-79001760, R. 8
September, 2010

©LEGEND is a registered trademark, and the Horse Logo is a trademark, of Meril.

©2015 Meril, Inc. All rights reserved.

Made in USA



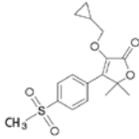
Equioxx® (firocoxib)

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 (NSAIDs). 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).

EQUIOXX may be given with or without food.

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 50-lb weight notch, aligning the arrow on the plunger with the notch on the ring, as shown in the pictogram.

2) Lock the ring in place by making ¼ turn to the right. Ensure it is locked (it should no longer slide).

Contraindications: Horses with hypersensitivity to firocoxib 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 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 Oral Paste with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. 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.

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.

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 firocoxib 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 activity¹ in animal models.

Based on *in vitro* horse data, 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 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.

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 individually-boxed syringes and packs of 72 individually wrapped syringes. Each syringe contains 6.93 grams of EQUIOXX paste, sufficient to treat a 1,250-lb. horse.

¹McCann 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;66(7):1278-1284

²McCann 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.

³Data on file.

Marketed by: Merial, Inc., Duluth, GA 30096-4640

Made in Brazil

For technical assistance or to report suspected adverse reactions, call 1-877-217-3543.

NADA 141-253, Approved by FDA

©2015 Merial, Inc. All Rights Reserved.

®EQUIOXX is a registered trademark of Merial.

Rev. 6-2015

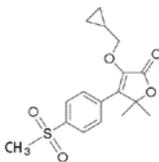
Equioxx[®]

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-(methylsulfonyl)phenyl)-5, 5-dimethylfuranone. The empirical formula is C₁₇H₂₀O₃S, 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 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 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_{1/2} 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 activity¹ 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 of 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;66(7):1278-1284.

² McCann ME, Anderson DR, Bideau 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
©EQUIOXX is a registered trademark of Merial.

©2011 Merial, Inc. All Rights Reserved.

Rev. 12-2011