Equine NSAID Best Practices

Non-steroidal anti-inflammatory drugs (NSAIDs) are typically used to treat conditions such as the pain and inflammation associated with equine osteoarthritis. Unlike NSAIDs used in human medicine, like ibuprofen, which can be purchased over-the-counter, NSAIDs in equine medicine are only available with a veterinarian’s prescription.

When prescribing an NSAID, your veterinarian will consider the type needed for the horse’s specific ailment. Each horse and each ailment is treated separately, depending on the horse’s individual response to the treatment. Fortunately, veterinarians have options when prescribing NSAIDs and will prescribe the best option for each individual horse. Veterinarians will take into account the ailment, age of the horse, activity level of the horse and the route of administration – some NSAIDs are available in injection, topicals, paste, powder or tablets.

While non-coxib NSAIDS have been used for years to treat equine osteoarthritis, EQUIOXX (firocoxib) is the only coxib NSAID approved for horses, and it controls the pain and inflammation associated with equine osteoarthritis. Horse owners and trainers have access to NSAIDs through their veterinarian with a prescription, and the veterinarian should be involved every time when determining if an NSAID should be used. Here are a few questions to ask your veterinarian if he or she determines an NSAID is needed:

1) What is the correct dosage and route of administration?
2) How often should the medication be administered?
3) When should I stop giving the medication?
4) How long before the medication takes effect?
5) Are there any side effects to this medication?
6) Should this medication be given with any other medications?

When giving any NSAID, it’s important to check dosage and administration guidelines. Talk to your veterinarian about NSAID options for your horse.

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.

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4 EQUIOXX product label.
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 a 2-3-cyclopropylmethoxy-4-4’-biphenylsulfonanilide, 3,5-dimethylpyrazole. The empirical formula is C₂₇H₂₄O₂N₂S, and the molecular weight is 358.5. 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 650 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/kg (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 depend 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 any other injectable material (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 only. Do not use in horses intended for human consumption.

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 hemostatic 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 foaliness, or lethargy are observed.

As a class, cyclooxygenase inhibitor 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 with existing renal, cardiovascular, and/or hepatic dysfunction.

Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandin that maintain normal homeostatic function. Such anti-inflammatory effects 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, concurrent 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 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 established 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 emesis and slurs of the gait, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Various adverse reactions associated with NSAIDs 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: 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 Tmax = 2.02 hours). The average plasma concentrations following equine Injection and oral administration were similar for 6 hours post-dose, after which the concentrations proceeded to decline in parallel. The terminal elimination half-life (16 ± 0.08 values) were not significantly different (p=0.03), 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 deacetylation/metathesis followed by glutamineacilation of that metabolite. Based upon radiolabel studies, the majority of firocoxib is eliminated in the urine as the glucuronide conjugate of the deacetylation/metathesized metabolite. Despite a high rate of plasma protein binding (89%), firocoxib exhibits a large volume of distribution (mean T1/2 = 1802 mL/kg). The drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 0-6 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 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). 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 5/8 horses demonstrated a white focus in the renal cortex which correlated with tubulo-interstitial nephropathy morphoccopy. The presence of tubulo-interstitial 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 (AST/ALT) were noted in all study groups at one or more timepoints. One male 3X horse with an elevated GGT value on Day 43 was noted to have tubulo-interstitial 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 15-35°C.

How Supplied: EQUIOXX (firocoxib) Injection for horses will be supplied in sterile, 25 ml amber vials for radio-dose use.


Made in Germany

NADA 141-313, Approved by FDA

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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 (NSAID). Firocoxib is a white crystalline powder described chemically as 3-cyclopropylmethylation-4-4-(4-methoxyphenyl)-3,5-dimethylfuranone. The empirical formula is C22H18ClNO4, and the molecular weight is 386.3. 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 osteoarthropathy in horses.

Dose 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/kg (0.1 mg/kg) of body weight once daily for up to 14 days.

Drug compatibility should be monitored in patients receiving concurrent drugs that may inhibit the metabolism of protein bound drugs with EQUIOXX Oral Paste.

Firocoxib is a select, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity in animal models. Based on in vitro horse data, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of inducible cyclooxygenase-2 (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 550 to 3,638 lb, 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 end, 84% of horses treated with EQUIOXX Oral Paste were judged improved on veterinarians’ clinical assessment, and 7.8% were also rated improved by owners. Horses treated with EQUIOXX Oral Paste showed improved in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was compatible 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 0.1, 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 findings in this study.

In another target animal study, firocoxib was administered orally to healthy adult horses (four males and castrates and four females per group) at 0.1, 0.3, 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 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 BMT, bilateral tubulointerstitial nephropathy and bilateral papillary necrosis.

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/kg (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: 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/kg (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: Excessive or ulcerations of the gums, tongue, lips and face, weight loss, colic, diarrhea, or ileus. 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/kg (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 mg/kg 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 body cells. The major metabolism mechanism of firocoxib in the horse is demethylcyclomethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of firocoxib is eliminated in the urine as the deoxycyclomethylated metabolite. Despite a high rate of plasma protein binding (99%), firocoxib exhibits a large volume of distribution (mean Vss = 1652 mL/kg). The terminal elimination half-life (T1/2) in plasma averages 30-40 hours after IV or oral paste dosing. Therefore, drug accumulation occurs with repeated dose administration and steady state concentrations are achieved beyond 5-6 daily oral doses in the horse. Dose linearity exists from 1.6X of 0.1 mg/kg/day.

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

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

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

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.

EQUIOXX Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthropathy in horses.
In the field trials, EQUIOXX Oral Paste was safely used concurrently with other therapies, including vaccines, antibiotics, and antihelminths. There were no significant interactions among the therapies. All horses were carefully monitored for signs of drug toxicity, and no adverse effects were noted.

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

**Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EQUIOXX n = 127</th>
<th>ACTIVE CONTROL n = 129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>2/127 (1.6%)</td>
<td>0/129 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0/127 (0%)</td>
<td>0/129 (0%)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1/127 (0.8%)</td>
<td>0/129 (0%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1/127 (0.8%)</td>
<td>0/129 (0%)</td>
</tr>
<tr>
<td>Uricemia</td>
<td>0/127 (0%)</td>
<td>0/129 (0%)</td>
</tr>
</tbody>
</table>

**In a target animal safety study conducted to support the approval of EQUIOXX Oral Paste (NADA 141-253), firocoxib was administered orally to healthy adult horses (four males or male castrates and six females) at 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 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 at 0.3 or 0.5 mg/kg. There were no other drug-related adverse findings in these field studies. In another target animal safety study, firocoxib was administered orally to healthy adult horses (four males or male castrates and four females each at 0.1, 0.3, and 0.5 mg firocoxib/kg body weight) at 3X, 10X, and 30X 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 at 0.1 mg/kg. There were no other drug-related adverse findings in these field studies.