Stop the Roller-Coaster Effect of Pain and Pain Relief

When it comes to non-steroidal anti-inflammatory drugs (NSAIDs), typically used to treat conditions such as the pain and inflammation associated with equine osteoarthritis,¹ horse owners look for treatment that performs on three levels:

- Safety.
- Consistency.
- Convenience.

Tried and True
EQUIOXX® (firocoxib) Brand Products have been tested on more horses in safety studies than any other NSAID,²,³ and remain the only NSAIDs approved by both the AQHA and the USEF for use up to 14 days.⁴,⁵,†

Consistent Therapy
Since some NSAIDs have a short half-life, meaning they leave the system fairly quickly, they require multiple doses each day.⁶ Multiple daily dosing can result in spikes and dips - possibly leaving the horse vulnerable to a roller-coaster effect of pain and pain relief. The active ingredient in EQUIOXX, firocoxib, has a longer half-life than other equine NSAIDs, so its levels stay steady for more hours, helping to eliminate this roller-coaster effect.⁷

EQUIOXX tablets and paste may be given with or without feed or hay.² With other NSAIDs, like phenylbutazone, feed — especially hay — delays time to peak effect.⁸,⁹

“With EQUIOXX, you can feel confident about achieving a consistent level of therapy for pain and inflammation relief throughout the entire day,” says Hoyt Cheramie, DVM, MS, Manager, Merial Large Animal Veterinary Services. “This means trainers and horse owners can spend less time worrying about whether or not the treatment is providing consistent relief and more time focusing on the horse.”

Three Choices, Same Proven Active Ingredient
EQUIOXX is the only coxib NSAID approved for horses, and it helps control joint pain and inflammation² associated with osteoarthritis with just one daily dose. EQUIOXX is available in three formulations: injection, paste, and tablet, allowing treatment to fit your horse’s specific needs.

- Injection (IV) is ideal to initiate therapy and is an excellent option for field and hospital settings.
- Paste is a convenient form for accurate dosing, especially for small horses and performances horses that are subject to testing.
- Tablets can be given with or without feed and are ideal for noncompetitive uses.
Talk to your veterinarian for more information and to discuss the best option for your horse.

*Joint pain and inflammation associated with equine osteoarthritis, also called degenerative joint disease.
† EQUIOXX Injection may be used for five of the 14 days.

**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.

**About Boehringer Ingelheim Animal Health**

On January 1st, 2017, Merial became part of the Boehringer Ingelheim group. As the second largest animal health business in the world, Boehringer Ingelheim is committed to making the industry even better at improving animal health. With more than 10,000 employees worldwide, Boehringer Ingelheim Animal Health has products available in more than 150 markets and a global presence in 99 countries. For more information about Boehringer Ingelheim Animal Health, click here.

**About Boehringer Ingelheim**

Boehringer Ingelheim is one of the world’s 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, Boehringer Ingelheim operates presently with a total of some 50,000 employees worldwide. The focus of the family-owned company, founded in 1885, is on researching, developing, manufacturing and marketing new medications of high therapeutic value for human and veterinary medicine. In 2015, Boehringer Ingelheim achieved net sales of about 14.8 billion euros. R&D expenditure corresponds to 20.3 per cent of net sales. For more information, please visit www.boehringer-ingelheim.com.

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2EQUIOXX product labels and FOI summaries and supplements.
3Data on file at Merial, Clinical Experience Report PHN 471, PR&D 0030701


7 Data on file at Merial, Pharmacokinetic Study, PR&D 0096601 and the PI for half-life.

8 Based on AUC (0-LOQ). Data on file at Merial, Systemic Drug Exposure Study, PR&D 0118201

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-(methylsulfanyl)phenyl]-5, 5-dimethylfuraneone. The empirical formula is C_{14}H_{15}NO_{3} and the molecular weight is 336.4 g/mol. The structural formula is shown to the right.

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

Indications:
EQUIOXX is indicated 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 0.044 mg/kg (0.09 mg/lb) of body weight once daily for up to 5 days. 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).

If further treatment is needed, EQUIOXX Oral Paste or EQUIOXX Tablets 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 recommended dosage of EQUIOXX Oral Paste 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 lbs 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).

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 left and slide the ring, as shown in the pictogram.

The recommended dosage of EQUIOXX Tablets is one 57mg tablet, for oral administration in horses weighing 600-1300lbs, once daily for up to 14 days.

The overall duration of treatment with any firocoxib formulation in horses, including EQUIOXX Injection, Oral Paste or Tablets will be dependent on the response observed, but should not exceed 14 days. EQUIOXX may be given with or without food.

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

Warnings:
EQUIOXX Tablets and Paste are for oral use in horses only. EQUIOXX Injection is for intravenous use in horses only. Do not use in horses intended for human consumption. Keep EQUIOXX Tablets out of the reach of dogs and other pets in a secured location in order to prevent accidental ingestion or overdose.

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 or ingestion.

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 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 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 with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein bound drugs with EQUIOXX has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of EQUIOXX has not been evaluated. Drug compatibility should be monitored in patients requiring adjutive therapy. The safe use of EQUIOXX in horses less than one year of 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:
The safety and effectiveness of EQUIOXX Tablets was supported by a relative bioavailability study comparing EQUIOXX Tablets to the EQUIOXX Oral Paste (See Clinical Pharmacology section), in animal pharmacokinetic information, and target animal safety for existing firocoxib-containing products in horses. The effectiveness of EQUIOXX Injection was established in a bio comparability study demonstrating that EQUIOXX Oral Paste is bioequivalent to EQUIOXX Injection. Thus additional studies were not performed to support the effectiveness of EQUIOXX Injection or Tablets, nor were additional studies conducted to support safety of EQUIOXX Tablets. The safety of EQUIOXX Injection was established through a target animal safety study of EQUIOXX Injection administered IV followed by EQUIOXX Oral Paste (See Animal Safety Section).

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/lb) 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.

Table 1: Adverse Reactions Seen in U.S. Field Studies with EQUIOXX Oral Paste

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EQUIOXX n = 127</th>
<th>Active Control n = 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Excitation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Loose stool</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Polyuria</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Uricaria</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

EQUIOXX Oral Paste was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics. Therefore based on relative bioavailability of firocoxib across formulations, concomitant use of EQUIOXX Injection or EQUIOXX Tablets with other therapies is expected to have the same safety profile.

The Safety Data Sheet (SDS) contains more detailed occupational safety information. To report suspected adverse events, for technical assistance, or to obtain a copy of the SDS, contact Merel at 1-877-217-3543. 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.

Information for Owner or Person Treating Horse: A Client Information Sheet should be provided to the person treating the horse. Treatment administrators and caretakers should be aware 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, and 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 Pharmacology:
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 Oral 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. A pharmacokinetic study was conducted to compare the relative bioavailability of an oral firocoxib tablet containing 57 mg firocoxib (EQUIOXX Tablets) to the paste formulation (EQUIOXX Oral Paste). The criteria for the Test/Reference (T/R) ratios and the 90% Confidence Intervals (CI) of EQUIOXX Tablets (test product) were adjusted on the basis of the safety and effectiveness data for EQUIOXX Oral Paste (reference product). The lower bound of the 90% CI for effectiveness was defined by the minimal effective plasma concentration in the study used to support the dosage characterization of EQUIOXX Oral Paste. Effectiveness was based upon the area under the plasma drug concentration-time curve to the last quantifiable concentration (AUClast), with the effectiveness criteria set at a T/R ratio of greater than or equal to 0.77 and a corresponding lower bound for the 90% CI of 0.71. The upper bound of the 90% CI for the safety setting was defined by the maximum safe plasma concentration (Cmax) in the study used to establish a margin of safety for EQUIOXX Oral Paste. Based upon that margin of safety, product safety was defined as a T/R of less than or equal to 1.53, with a corresponding upper bound for the 90% CI of 1.71.
The relative bioavailability study was a randomized, two period, two sequence crossover study in thirty horses. Each horse received a single tablet (57 mg firocoxib) and a single tube of paste (56.7 mg firocoxib). Blood samples were collected at 15 minutes, 45 minutes, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 32, 46, 72, 96 and 120 hours following each treatment. Samples were analyzed by LC-MS/MS for firocoxib concentrations. The results of the relative bioavailability study are summarized in Table 2. The Cmax and AUClast of EQUIOXX Tablets were within the adjusted 90% CI for safety and effectiveness and met the criteria established for successfully demonstrating that EQUIOXX Tablets and EQUIOXX Oral Paste are acceptable as pharmaceutical alternatives.

There was a substantial difference in the Tmax (time to maximum plasma concentration) between EQUIOXX Oral Paste and EQUIOXX Tablets. The Tmax ranged from 0.25-4.5 hours for EQUIOXX Oral Paste and 0.25-12 hours for EQUIOXX Tablets. The difference in the rate and extent of absorption was greatest within the first three hours after administration. The mean terminal elimination half-life of EQUIOXX Oral Paste (45.45 hours) was similar to that of EQUIOXX Tablets (44.49 hours).

### Table 2: Relative Bioavailability Results for EQUIOXX Oral Paste (Reference) and EQUIOXX Tablets (Test) (=30 horses)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Reference</th>
<th>Geometric Mean</th>
<th>Test</th>
<th>Geometric Mean</th>
<th>Test/Reference</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>ng/mL</td>
<td>78.44</td>
<td>58.85</td>
<td>0.75</td>
<td>67.92</td>
<td>92.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUClast</td>
<td>hr*ng/mL</td>
<td>2515.77</td>
<td>2336.32</td>
<td>0.93</td>
<td>86.37</td>
<td>99.85</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cmax = maximum observed plasma concentration

AUClast = Area Under the Curve to the last quantifiable time point

CI = Confidence Interval

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 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 (1/2) of equiproxy was not significantly different (p>0.05), with values ranging from 14.6 to 80.0 hours (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 decyclodupropylmethylation followed by glucuronidation of that metabolite. Based on radioisotope studies done for the firocoxib formulation, the majority of firocoxib is eliminated in the urine as the glucuronide conjugate of decyclodupropylmethylated 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 (T1/2) in plasma averages 30-40 hours after IV, oral paste or tablet 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 1-2X of 0.1mg/kg/day after oral administration. 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)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.

The effectiveness of EQUIOXX Tablets and EQUIOXX Injection were established in relative bioavailability studies comparing these to EQUIOXX Oral Paste. Therefore additional field studies were not performed to support the effectiveness of EQUIOXX Tablets or EQUIOXX Injection. See Clinical Pharmacology.

### Animal Safety:
In a target animal safety study conducted to support the approval of EQUIOXX Oral Paste, 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 safety 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 formation 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 (MBBT), and a dilated pupils 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 MBBT, 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 MBBT. 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.

### References:
3 Data on file.