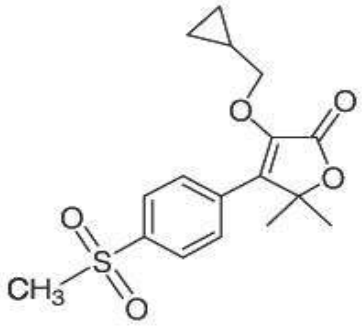
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Firocoxib

Background

Firocoxib is a non-steroidal anti-inflammatory (NSAID). It is assigned a 4/C classification by the ARCI. Firocoxib is currently licensed for use in horses as EQUIOXX® (Merial Limited, Duluth, Georgia). EQUIOXX® is available as an oral paste (0.82%), a solution for parenteral administration and in tablet formulation.[i] It is administered both orally and parenterally for its anti-inflammatory and analgesic effects.[ii] It has been used to treat clinical signs of osteoarthritis and fever, pain, and inflammation caused by other non-orthopedic conditions.[iii] Firocoxib is a prescription medication and can only be dispensed by, or upon the request of a veterinarian.



https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=28449

Firocoxib is a selective cyclooxygenase-2 (COX-2) inhibitor. It possesses a more favorable toxicity profile than other NSAIDs such as phenylbutazone and flunixin that are not selective for COX-2. Cyclooxygenase (COX) has an important role in the production of prostaglandins – highly active biologic compounds found in all types of mammalian tissues that facilitate intercellular communication of various processes. Inhibiting COX blocks prostaglandin synthesis and prostaglandin-mediated effects, including inflammation. Though inflammation is a beneficial response that protects injured tissues, if left untreated it can contribute to the pathogenesis of numerous diseases.[iv]

Most causes of pain are mediated by inflammation; this has made NSAIDs the analgesic agents most commonly used in horses worldwide.[v] However, the use of NSAIDs has been associated adverse effects including gastrointestinal ulceration, hypoproteinemia, and renal papillary necrosis. In the 1990s, multiple isoforms of COX were discovered.[vi] COX-1 is constitutively expressed in most tissues and is responsible for controlling multiple physiological processes such as platelet aggregation, vasodilation in the kidneys, and production of the protective mucous coating the gastrointestinal tract. COX-2 is mainly expressed during inflammatory states and is primarily involved in the pathological responses of inflammation.[vii]

Firocoxib is a COX-1 sparing drug that is approximately 265 times more selective in inhibiting COX-2 than COX-1. This selective COX-2 inhibitor offers the anti-inflammatory benefits of traditional NSAIDs without the adverse effects associated with COX-1 inhibition. Firocoxib is administered once daily which, combined with its limited adverse effects, has advanced its popularity.[viii]

Studies have determined firocoxib to be as effective as phenylbutazone in treating inflammation related to surgery, osteoarthritis, general lameness, colic, and ocular inflammation.[ix] Additionally, it has been found effective in foals but with a shorter half-life.[x] However, studies have also shown COX-2 selective inhibitors may not be as beneficial in horses with preexisting gastric ulcers because of an indicated housekeeping function of COX-2 in the healing process of ulcers. Studies have also indicated a potential delay in gastrointestinal healing and adverse effects on the kidneys and bones from firocoxib use.[xi]

Administration Study

This study was performed by personnel in the Maddy Equine Analytical Pharmacology Laboratory (Davis, CA) under the direction of Dr. H. Knych. Nine horses (geldings and mares), including 3 Thoroughbreds, 4 Quarter Horses, one Westphalian and one Dutch Warmblood, were split in a balanced 3-way crossover design experiment. Three horses were administered the injectable formulation of firocoxib as Equioxx® intravenously a dose of 0.09 mg/kg once daily for 5 days. The next group received the Equioxx® oral paste formulation at 0.1 mg/kg once daily for 14 days. The final group received a 57 mg total dose (approximately 0.1 mg/kg) once daily for 14 days of Previcox®, a firocoxib tablet formulation with FDA-approval for use in dogs. Tablets were dissolved in approximately 4-5 ml of water and administered orally via dosing syringe. (Subsequent to this study, firocoxib in tablet formulation as Equioxx® received FDA approval for use in horses. Therefore, off-label use of Previcox® is no longer warranted.)

The dosage amounts and durations of the injectable and paste formulations were based upon the label dose and manufacturer's recommended maximum duration of administration. The tablet dose was selected based upon the most common dose reported by equine practitioners. The horses were given a minimum two week wash out period, following the confirmation of non-detectable plasma concentrations, between each of the subsequent administration protocols.

Blood samples were obtained immediately before dose administration and at .25, .5, and .75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours post administration following dosing on the first and last days of the treatment schedule. (For IV administration, the final dose was administered on Day 5; for oral dosing, the final dose was administered on Day 14.) Blood samples for IV administration were also collected at 5- and 10-minutes post-administration. Additional samples

were collected every 12 hours throughout the dosing period, with morning samples collected prior to the once daily administration. Additional samples were collected following the final dose at 12-hour intervals for seven days and once daily thereafter until plasma concentrations were below the Limit of Detection (LOD).

Extraction and Analysis Procedures

Quantification of firocoxib in plasma was performed at the Clinical Pathology Laboratory of the William R. Pritchard Veterinary Medical Teaching Hospital of the University of California (Davis, CA) using validated methods. Plasma concentrations were measured by liquid chromatography-mass spectrometry (LC-MS) using LTQ Orbitrap XL with an Acuity chromatography system. The LC-MS used an analytical reference standard (Toronto Research Chemicals) and a deuterated standard, Firocoxib-*d*-$_6$ (Witega) was used to improve precision and accuracy. The method was optimized to provide a Limit of Quantification (LOQ) of 0.1 ng/ml and an LOD of approximately 0.05 ng/ml.

Pharmacokinetic Modeling

Pharmacokinetic analysis was performed on firocoxib plasma concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, St. Louis, MO).

Results and Discussion

There were large fluctuations between maximum and minimum plasma concentrations following the first administration, however as a steady state was achieved the degree of fluctuation decreased over time. Steady state plasma concentrations were not achieved by the end of the 5 consecutive IV administration but were achieved by the 10th day following both oral formulations.

Average concentrations of firocoxib were below the LOD by Day 21 for injectable administration, and by Day 29 for paste and tablet administrations. (Table 1.1)[xii].

Table 1.1 Detection times for firocoxib in plasma following IV (0.09 mg/kg bwt s.i.d. × 5 days) and oral administration of paste (0.1 mg/kg bwt s.i.d. × 14 days) and tablets (57 mg s.i.d. × 14 days) to horses (n = 9). All values in this table were generated using noncompartmental analysis

	Intravenous		Oral paste		Oral tablets	
	Mean (± S.D.)	**Median (Range)**	**Mean (± S.D.)**	**Median (Range)**	**Mean (± S.D.)**	**Median (range)**
Days Until Time Of Last Detected Plasma Concentration	20.7 (± 3.20)	20.0 (17.0–25.0)	29.3 (± 8.43)	27.0 (22.0–41.0)	29.1 (± 7.41)	30.0 (22.0–40.0)

Scientific Advisory Committee Recommendation

The historical threshold, as previously recommended by the RMTC was 20 ng/mL of firocoxib in plasma which had corresponding withdrawal guideline of 14 days and was based on 0.1 mg/kg administered orally once daily for four days. This threshold had been selected in order to prevent a single administration of firocoxib at less than 48 hours to a race.

In December 2019, the ARCI adopted a Model Rule that included a 48-hour restricted administration for all NSAIDs and a prohibition on stacking (the detection of two or more NSAIDs in a blood and/or urine sample.) Concurrent with this was the withdrawal of the 20 ng/mL plasma threshold for firocoxib.

Veterinarians and horsemen are advised to refer to the RMTC Advisory NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs): 48-hour Restricted Administration Time and Prohibition on Stacking[MS1][MS2] for additional withdrawal guidance.

Practice Tips

Different formulations of firocoxib, administration of higher doses, use of other routes of administration, longer durations of treatment, or combinations of firocoxib with other substances represent unknown risk for a concentration in excess of the threshold and therefore an extended withdrawal time is recommended. Veterinarians are advised to use caution when deviating from doses and routes that have been studied and to use an extended withdrawal time and/or submit a sample for analysis prior to competition.

For all study administration protocols the plasma half-life of firocoxib was greater than 1.5 days, and the range of times from final treatment to plasma concentrations <LOD was highly variable between the study horses. To avoid risk of a NSAID stacking violation, clearance testing of both blood and urine is strongly recommended prior to entry when a horse has been treated with firocoxib.

Firocoxib is a COX-2 selective inhibitor and may not possess the same side effects as traditional NSAIDs. Veterinarians, however, should note that it may not be effective with some preexisting conditions, such as ulcers; cause a potential delay in gastrointestinal healing; and have adverse effects on the kidneys and bones.

Note: With the commercial availability of Equioxx tablets (with FDA-approval for use in the horse) the extra-label use of Previcox is not permitted.

References

[i] Plumb, Donald, *Plumb's Veterinary Drug Handbook, Eighth Edition,* p. 604.

[ii] *Id.* at 602.

[iii] *Id.*

[iv] Kvaternick, V., *et al, Pharmacokinetics and Metabolism of Orally Administered Firocoxib, a Novel Second Generation Coxib, in Horses,* J. Vet. Pharmacol. Therap. 30: 208-217 (2007), DOI: 10.1111/j.1365-2885.2007.00840.x.

[v] Sanchez, L.C., *et al*, *Pain Control in Horses: What Do We Really Know?,* Equine Vet. J. 46: 517-523 (2014), DOI: 10.1111/evj.12265.

[vi] Hovanessian, N., *et al*, *Pharmacokinetics and Safety of Firocoxib after Oral Administration of Repeated Consecutive Doses to Neonatal Foals,* J. Vet. Pharmacol. Therap. 37: 243-251 (2013), DOI: 10.1111/jvp.12082.

[vii] Barton, M.H., *et al*, Efficacy of Cyclo-Oxygenase Inhibition by Two Commercially Available Firocoxib Products in Horses, Equine Vet. J., 46: 72-75 (2014).

[viii] *Id.*

[ix] Doucet, M.Y., *et al, Comparison of Efficacy and Safety of Paste Formulations of Firocoxib and Phenylbutazone in Horses with Naturally Occuring Osteoarthritis,* JAVMA, 232(1): 91-97 (2008); Hilton, H.G., *et al, Distribution of Flunixin Meglumine and Firocoxib into Aqueous Humor of Horses,* J. Vet. Intern. Med., 25: 1127-1133 (2011); Cook, V.L., *et al, Effect of Fircoxib or Flunixin Meglumine on Recovery of Ischemic-injured Equine JeJunum,* AJVR 70(8): 992 -1000 (2000); Duz, M., *et al*, *Effect of Flunixin Meglumine and Firocoxib on Ex Vivo Cyclooxygenase Activity in Horses Undergoing Elective Surgery,* AJVR, 76(3): 208 -215 (2015); Orsini, J.A., *et al, Evaluation of Oral Administration of Firocoxib for the Management of Musculoskeletal Pain and Lameness Associated with Osteoarthritis in Horses,* AJVR 73(5): 664 – 671 (2012).

[x] Hovanessian, N., *et al*, *Pharmacokinetics and Safety of Firocoxib after Oral Administration of Repeated Consecutive Doses to Neonatal Foals,* J. Vet. Pharmacol. Therap. 37: 243-251 (2013), DOI: 10.1111/jvp.12082.

[xi] Letendre, L.T., *et al*, *Pharmacokinetis of Firocoxib After Administration of Mulitple Consecutive Daily Doses to Horses,* AJVR, 69(11): 1399- 1405 (2008).

[xii] Knych, H.K., *et al, Detection and Pharmacokinetics of Three Formulations of Firocoxib Following Multiple Administrations to Horses,* Equine Vet. J. (2014), DOI: 10.1111/evj.12211.