Date of Approval: July 24, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-458

EQUIOXX

firocoxib

Tablets

Horses

EQUIOXX Tablets are administered once daily for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

Sponsored by:

Merial, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-458

B. Sponsor

Merial, Inc.
3239 Satellite Blvd.
Bldg. 500
Duluth, GA 30096-4640

Drug Labeler Code: 050604

C. Proprietary Name

EQUIOXX

D. Product Established Name

Firocoxib

E. Pharmacological Category

Non-steroidal anti-inflammatory

F. Dosage Form

Tablet

G. Amount of Active Ingredient

57 mg firocoxib

H. How Supplied

The product is available as 57 mg round half-scored tablets in 60 and 180 count bottles and a 30 count carton, which contains three 10 count blister packs.

I. Dispensing Status

Rx

J. Dosage Regimen

Administer one 57 mg tablet daily for horses weighing 800-1300 lbs for up to 14 days duration.

K. Route of Administration

Oral

L. Species/Class

Horses

M. Indication

EQUIOXX Tablets are administered once daily for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

II. EFFECTIVENESS

A. Dosage Characterization

The dosage of EQUIOXX Tablets was based upon the dosage characterization of EQUIOXX (firocoxib) Oral Paste (NADA 141-253). A relative bioavailability study was conducted to demonstrate that EQUIOXX Tablets and EQUIOXX Oral Paste were acceptable as pharmaceutical alternatives. Please refer to the Freedom of Information (FOI) Summary for the original approval of EQUIOXX Oral Paste, dated December 30, 2005, for complete dosage characterization information.

B. Substantial Evidence

The requirements for substantial evidence of effectiveness and target animal safety were fulfilled by a pharmacokinetic study (PR&D 0313601) comparing the relative bioavailability of an oral firocoxib tablet containing 57 mg firocoxib to a single 56.8 mg firocoxib dose of the approved 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 of 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 dose characterization of EQUIOXX Oral Paste, Study PR&D 0036901: A Dose Titration Study of ML-1,785,713 Oral Paste in Horses[1]. 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 set at 0.71. The upper bound of the 90% CI for safety was defined by the maximum safe plasma concentration (Cmax) in the study used to establish a margin of safety for EQUIOXX Oral Paste, Study PR&D 0139501: A Study to Evaluate the Safety of an Injectable Solution of Firocoxib Administered Intravenously Followed by an Oral Paste Formulation of Firocoxib at the Recommended Dose (1,3, and 5X) in Horses[2]. 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.

[1] Described further in: FOI Summary for the original approval of EQUIOXX Oral Paste, NADA 141-253, dated December 30, 2005

[2] Described further in: FOI Summary for the original approval of EQUIOXX Injection, NADA 141-313, dated August 20, 2010

1. Pharmacokinetic Study (Relative Bioavailability Study)

   Title: A Two Period Crossover Study to Demonstrate Bioequivalence in Horses Between a Firocoxib Oral Paste and a Firocoxib Oral Tablet. (Study No. PR&D 0313601)

   Study Dates: November 2014-December 2014

   Study Location: Fulton, MO, USA

   Study Design:

   Objective: To demonstrate the relative bioavailability between an oral firocoxib tablet (1 tablet containing 57 mg firocoxib per horse) and an oral firocoxib paste (1 syringe containing 56.8 mg firocoxib per horse).

   Study Animals: Thirty healthy horses (female and male castrate) of varying breeds were enrolled in the study. Enrolled horses ranged in age from 2-15 years old and ranged in weight from 849 - 1305 lbs.

   Experimental Design: The thirty horses were randomized into two groups of 15 horses each. One horse from each group (replicate) was then assigned to either Treatment sequence 1 or Treatment sequence 2 as described below in the drug administration section.

   Drug Administration: All horses were weighed prior to treatment to ensure they were within the intended weight bracket. Tablets were administered by placing one 57 mg tablet on a small amount of feed in a bucket. A small amount of feed was offered after treatment with paste. The treatment sequences are described below.

   Treatment Sequence 1:
   One firocoxib tablet was administered on Day 0 (period 1), and a full syringe of firocoxib oral paste was administered on Day 28 (period 2).

   Treatment Sequence 2:
   One full syringe of firocoxib oral paste was administered on Day 0 (period 1), and one firocoxib tablet was administered on Day 28 (period 2).

   Measurements and Observations: All treated horses were observed hourly for the first four hours after treatment. The condition of the horses' oral mucosa was evaluated periodically over the first 5 days following treatment. The study director and personnel conducting the daily health, oral cavity observations, and data collection were blinded to treatment and sequence.

   Blood Samples were taken from all treated horses at the following intervals after treatment: 15 minutes, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, and 120 hours. Plasma was recovered from each blood sample and analyzed for firocoxib using a validated protein precipitation liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) method.

Pharmacokinetic and Statistical Methods: Non-compartmental pharmacokinetic parameters were determined for each individual horse using Phoenix 64 WinNonlin version 6.3 (Pharsight Corp.). The AUClast value for each horse was estimated using the linear trapezoidal method. The Cmax was the highest observed plasma concentration for each horse.

The pharmacokinetic variables used to estimate relative bioavailability were Cmax and AUClast. Cmax and AUClast were logarithmically transformed prior to analysis. Plasma concentrations and pharmacokinetic variables were analyzed using a general linear mixed model in SAS. The fixed effects were sequence, period, and formulation. The random effects were subject nested within sequence and replicate. The criteria for safety and effectiveness were an adjusted T/R ratio of 1.53 and 90% CI lower bound of 1.37 and upper bound of 1.71 for Cmax and a T/R of 0.77 and 90% CI lower bound of 0.71 and upper bound of 0.84 for AUClast.

Results: The results of the relative bioavailability study are summarized in Table 1. The 90% CIs for Cmax and AUClast were 67.92-82.88, and 86.37-99.85, respectively. The Cmax and AUClast of the firocoxib tablet were within the adjusted T/R ratios and 90% CI criteria established for confirming product safety and effectiveness; the Cmax did not exceed the upper 90% CI for safety and the AUClast exceeded the lower 90% CI for effectiveness. Therefore, EQUIOXX Tablets and EQUIOXX Oral Paste are acceptable as pharmaceutical alternatives.

Table 1: Relative Bioavailability Results for EQUIOXX Oral Paste (Reference) and EQUIOXX Tablets (Test) (n=30 horses)

Parameter	Units	Reference Geometric Mean	Test Geometric Mean	Test/Reference	Lower 90% CI	Upper 90% CI
Cmax	ng/mL	78.44	58.85	0.75	67.92	82.88
AUC last	hr*ng/mL	2515.77	2336.32	0.93	86.37	99.85

Cmax = maximum observed plasma concentration
AUClast = Area Under the Curve to the last quantifiable time point
CI = Confidence Interval

The mean (SD or range) of the primary pharmacokinetic parameters of interest are summarized in Table 2. There was a substantial difference in the Tmax (time to maximum plasma concentration) between the paste and tablets. The Tmax ranged from 0.25-4 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 paste (45.45 hours) was similar to that of the tablet (44.49 hours).

Table 2: Mean (SD or range) Pharmacokinetic Parameters of EQUIOXX Oral Paste and EQUIOXX Tablets (n=30 horses)

Parameter	EQUIOXX Oral Paste	EQUIOXX Tablets
Cmax (ng/mL)	96.12 (26.69)	75.34 (21.46)
Tmax (hr)	1.092 (range 0.25-4)	2.43 (range 0.25-12)
AUClast (ng*hr/mL)	3139.14 (988.20)	3029.58 (971.81)
AUCinf (ng*hr/mL)	3760.79 (1230.13)	3618.439 (1159.64)
AUC_%Extrap_obs (ng*hr/mL)	15.29 (range 4.63-50.16)	15.88 (range 4.46-37.64)
t 1/2 lambda (hr)	45.45 (22.17)	44.49 (14.51)

Cmax = maximum observed plasma concentration
Tmax = time to maximum concentration
AUClast = Area Under the Curve to the last quantifiable time point
AUCinf = Area Under the Curve extrapolated to infinity
AUC_%Extrap_obs = percentage of the area under the curve extrapolated to infinity
t ½ lambda = terminal elimination half-life

Adverse Reactions: Horses were observed daily for adverse reactions, which included oral cavity examinations. Oral ulceration is a known adverse event associated with NSAID administration in horses. Varying degrees of oral ulcerations, lesions, or other minor abnormalities were seen during the study, but these abnormalities were not directly attributable to treatment with EQUIOXX Oral Paste or EQUIOXX Tablets. No adverse reactions attributable to treatment with EQUIOXX Oral Paste or EQUIOXX Tablets occurred during the study.

Conclusions: The Cmax and AUClast of EQUIOXX Tablets were within the adjusted 90% CI for safety and effectiveness. Therefore, EQUIOXX Tablets have met the criteria established for successfully demonstrating that the EQUIOXX Tablets and EQUIOXX Oral Paste will have equivalent safety and effectiveness profiles and are acceptable as pharmaceutical alternatives.

The FOI Summary for the original approval of NADA 141-453 dated December 30, 2005, contains a summary of studies that demonstrate the effectiveness of EQUIOXX (firocoxib) Oral Paste for horses.

III. TARGET ANIMAL SAFETY

The safety of EQUIOXX Tablets is supported by a pharmacokinetic study comparing the relative bioavailability of EQUIOXX Tablets to EQUIOXX Oral Paste (see CLINICAL PHARMACOLOGY, Relative Bioavailability Study), pharmacovigilance information, and target animal safety study information for existing firocoxib containing products in horses. No additional target animal safety studies were conducted with EQUIOXX Tablets.

The FOI Summaries for the original approvals of NADA 141-253 dated December 30, 2005, and NADA 141-313 dated August 20, 2010, contain a summary of target animal safety studies in horses.

IV. HUMAN FOOD SAFETY

This drug is intended for use in horses. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

The product labeling contains the following Warning statement: Do not use in horses intended for human consumption

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to EQUIOXX:

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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that EQUIOXX, when used according to the label, is safe and effective for the control of pain and inflammation associated with osteoarthritis in horses.

A. Marketing Status

This product is restricted to use by or on the lawful order of a licensed veterinarian because professional expertise is needed in the diagnosis and treatment of osteoarthritis in horses, and to monitor the safe use of the product including treatment of any adverse reactions.

B. Exclusivity

EQUIOXX, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C Act.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.