

Date of Approval: December 30, 2005

FREEDOM OF INFORMATION SUMMARY

NADA 141-253

EQUIOXX Oral Paste

0.82 % firocoxib (w/w)

EQUIOXX Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

Sponsored by:

Merial Limited
3239 Satellite Blvd.
Duluth, GA 30096

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I. GENERAL INFORMATION:

- a. File Number: NADA 141-253
- b. Sponsor: Merial Ltd.
3239 Satellite Blvd., Bldg. 500
Duluth, GA 30096-4640
Drug Labeler Code: 050604
- c. Established Name: firocoxib
- d. Proprietary Name: EQUIOXX Oral Paste
- e. Dosage Form: Oral Paste
- f. How Supplied: EQUIOXX Oral Paste is available in packs of 20, 72 and 216 individually-boxed syringes.
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each syringe contains 6.93 grams of 0.82% w/w firocoxib paste, sufficient to treat a 1250 lb horse.
- i. Route of Administration: Oral
- j. Species/Class: Equine
- k. Recommended Dosage: 0.045 mg/lb (0.1 mg/kg) body weight daily for up to 14 days
- l. Pharmacological Category: Nonsteroidal anti-inflammatory
- m. Indications: EQUIOXX Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

2. *EFFECTIVENESS*

a. Dosage Characterization:

Two studies were conducted in support of the dosage characterization for the oral, once-daily 0.1 mg/kg dose of firocoxib (0.82% w/w) paste in horses.

- (1) Study PR&D 0036901: A Dose Titration Study of ML-1,785,713 Oral Paste in Horses.

In this study, firocoxib oral paste was administered to a total of 18 horses (6 per treatment group) with lameness, at doses of 0.0625 (using 0.51% w/w formulation), 0.125 (using 1.03% w/w formulation), or 0.25 mg/kg (using 2.05% w/w formulation) once daily for seven days. Clinical observations were recorded at baseline (pre-treatment) and on Days 0, 2, and 6 (approximately 12 hours post-treatment). Primary clinical endpoints were peak vertical force (measured by force plate analysis) and lameness score. Plasma firocoxib concentrations were measured after the 1st, 3rd, and 7th doses at approximately 2, 12, and 24 hours post-dose. Clinical results indicated improvement relative to baseline at all three dose levels, with greater improvement at the 0.125 and 0.25 mg/kg doses. Dose linearity along with significant plasma drug accumulation was demonstrated among the three doses. This is consistent with the long half life (30-34 hours) of the firocoxib paste formulation in horses.

- (2) Study PR&D 0065801/02: A Dose Titration Study of ML-1,785,713 Oral Paste in Horses.

In this study, firocoxib oral paste was administered to a total of 64 horses (16 per group) with lameness, at doses of 0.0, 0.05, 0.10, and 0.25 mg/kg once daily for seven days. Clinical observations were recorded at baseline (Day -1) and on Days 0, 2, and 6 (approximately 10 hours post-treatment). The primary clinical endpoints were the lameness score and peak vertical force. Plasma firocoxib concentrations were measured after the 1st, 3rd and 7th doses at approximately 10 and 24 hours post-dose. Clinical results indicated improvement in lameness and peak vertical force scores for both 0.1 and 0.25 mg/kg doses. Again, dose linearity along with significant plasma drug accumulation was observed among the doses.

The 0.1 mg/kg dose was selected for further study.

b. Substantial Evidence:

A multicenter field study was conducted at nine sites to demonstrate the effectiveness and safety of firocoxib administered for 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

(1) Field Study (PR&D 000084201-07, 09-10)

Title: PR&D 00842: A Study to Assess the Efficacy, Safety and Acceptability of ML-1,785,713 Oral Paste in Horses for the Control of Pain and Inflammation Associated with Osteoarthritis Under Field Conditions

(a) Type of Study: Active-controlled, Masked, Randomized Field Studies

(b) Investigators:

Investigators	Locations
Dr. Michèle Doucet	Montreal, Québec, Canada
Dr. Faith Hughes	Ocala, FL
Dr. Craig Reinemeyer	Knoxville, TN
Dr. Charles MacAllister	Stillwater, OK
Dr. Roger Sifferman	Springfield, MO
Dr. Scott McClure	Ames, IA
Dr. Dean Hendrickson	Fort Collins, CO
Dr. Gary White	Sallisaw, OK
Dr. Alicia L. Bertone	Columbus, OH

(c) General Design:

- (1) Purpose: The objective of this study was to demonstrate, under field use conditions, the effectiveness, safety and acceptability of firocoxib administered for 14 days for the control of pain and inflammation associated with osteoarthritis in horses.
- (2) Test Animals: 253 client-owned horses of various breeds were enrolled. Effectiveness was evaluated in 240 horses and safety was evaluated in 252 horses. The horses ranged in age from 2 to 37 years and weighed from 595 to 1638 lbs. One hundred twenty-seven horses received firocoxib, and 126 received phenylbutazone.
- (3) Control: Phenylbutazone 20% w/w oral paste for horses
- (4) Diagnosis: Enrolled horses were diagnosed with osteoarthritis by radiographic evidence within the preceding 29 days. Navicular degeneration was also included with radiographic evidence of prominent bony change.

The most severely affected limb at the initial visit was assessed at all evaluations for the duration of the study.

- (5) Dosage Form: Final market formulation of firocoxib (0.82% w/w) oral paste for horses
- (6) Route of Administration: Oral
- (7) Dosages Used: 0.045 mg/lb (0.1 mg/kg) body weight of firocoxib administered once daily; 1.0 g/500 lb body weight of phenylbutazone administered once daily
- (8) Treatment Duration: 14 days
- (9) Variables Measured: The Investigator conducted general health and physical examinations and lameness evaluations at the initial visit (V1: Day -4 to Day 1), at the study midpoint (V2: approximately Day 7), and at the study endpoint (V3: approximately Day 14). Serum chemistry was evaluated at V1, V2 and V3; hematology was evaluated at V1 and V3. The primary variable of effectiveness was clinical improvement in lameness as assessed by the Investigator at study endpoint (V3). Improvement was defined as one of the following:
 - a. Reduction of at least 1 in overall lameness score, and/or
 - b. Combined reduction of at least 3 in scores for joint swelling, range of motion, and pain on palpation/manipulation as assessed by the Investigator.

Overall lameness, pain on palpation or manipulation, range of motion and joint swelling were assessed at the three scheduled time points and scored as follows:

Overall Lameness Score (Based on American Association of Equine Practitioners (AAEP) Scoring System)

Grade 0: No lameness

Grade 1: Difficult to observe; not consistently apparent regardless of circumstances (e.g., carrying weight, circling, incline, hard surface, etc.)

Grade 2: Difficult to observe at a walk or trotting in straight line; consistently apparent under certain circumstances (e.g., carrying weight, circling, incline, hard surface, etc.)

Grade 3: Consistently observable at a trot under all circumstances

Grade 4: Obvious lameness, marked nodding, hitching or shortened stride

Grade 5: Minimal weight bearing in motion and/or at rest; inability to move

Joint circumference of the most severely affected joint and the contralateral joint were measured with a tape and assessed clinically. Joints that could not be measured (e.g., coffin joint) were assigned a missing score and were not analyzed.

Joint Swelling Score (Measurement as compared to joint of contralateral limb)

- 0 = No swelling (circumference not more than 3% larger than contralateral limb)
- 1 = Mild swelling (fibrosis or mild, palpable fluid distension; >3 to 10% larger than contralateral limb)
- 2 = Moderate swelling (obvious, palpable fluctuant fluid distension; >10 to 20% larger than contralateral limb)
- 3 = Severe swelling (pronounced, palpable firm fluid distension; >20% larger than contralateral limb)

Investigator Assigned Swelling Score (Clinical assessment)

- 0 = No swelling or not applicable
- 1 = Mild swelling (fibrosis or mild, palpable fluid distension)
- 2 = Moderate swelling (obvious, palpable fluctuant fluid distension)
- 3 = Severe swelling (pronounced, palpable firm fluid distension)

Range of Motion Assessment (Most severely affected limb)

- 0 = Normal
- 1 = Slightly reduced (< 25% reduction as compared to expected normal range of motion)
- 2 = Moderately reduced (25 – 50% reduction as compared to expected normal range of motion)
- 3 = Severely reduced (> 50 % reduction as compared to expected normal range of motion)

Pain on Manipulation or Palpation

- 0 = No response to firm pressure
- 1 = Mild pain (exhibits muscle tremors and/or slight avoidance movement in response to digital palpation or compression)
- 2 = Moderate pain (definite limb withdrawal in response to digital palpation or compression)
- 3 = Severe pain (marked withdrawal from attempted digital palpation or compression)

Owners subjectively scored improvement from the initial visit (V1) on approximately Days 7 and 14. Owners made daily health observations and assessed convenience of administration and acceptability of treatment on approximately Day 14.

Owner Assessment Criteria for Improvement

- 2 = Improved from initial visit
- 1 = No change from initial visit
- 0 = Worsened from initial visit

(d) Results: Two hundred fifty-three client-owned horses of various breeds were enrolled in the study. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Thirteen horses were dropped from the effectiveness evaluation for protocol non-compliance and 1 horse was dropped from the safety evaluation for protocol non-compliance. Of the 13 horses dropped from the effectiveness evaluation, 8 were in the active control treated horses and 5 were in the firocoxib treated horses. The 1 horse dropped from the safety evaluation was treated with the active control.

Treatment with 0.1 mg/kg firocoxib orally once daily resulted in overall clinical improvement that was comparable to the active control, phenylbutazone, at both study midpoint (Day 7) and endpoint (Day 14). Both treatment groups showed clinical improvement from the initial visit. The results are summarized in Table 1.

Table 1. Veterinarian Clinical and Non-Inferiority Evaluation

Group	Percentage of Horses with Overall Clinical Improvement in Lameness	
	Day 7 (Visit 2)	Day 14 (Visit 3)
Treatment		
Firocoxib (n=122)	82.0%	84.4%
Phenylbutazone (n=118)	83.9%	86.4%
Difference (Control-Test Article)	1.9%	2.0%
Is non-inferiority demonstrated? (Margin of difference is <15%)	Yes	Yes

Tables 2 and 3 summarize the percentage of horses that showed improvement from the initial visit for the secondary efficacy variables (lameness, pain on manipulation, joint swelling (observed), joint swelling (calculated), range of motion) at Visit 2 and Visit 3.

Table 2. Percentage of Horses Improved at Day 7 (\pm 3 days) Veterinarian Evaluation

Variable	Percentage of Horses Showing Improvement @ Day 7	
	Firocoxib (n=122)	Phenylbutazone (n=118)
Lameness	80.3%	83.1%
Pain on manipulation	59.2%	53.0%
Joint swelling (observed)	22.1%	15.2%
Joint swelling (calculated)	25.6%	11.2%
Range of motion	36.4%	24.6%

Table 3. Percentage of Horses Improved at V3 Veterinarian Evaluation

Variable	Percentage of Horses Showing Improvement @ Day 14	
	Firocoxib (n=122)	Phenylbutazone (n=118)
Lameness	83.6%	85.6%
Pain on manipulation	65.0%*	49.6%
Joint swelling (observed)	23.0%	25.4%
Joint swelling (calculated)	24.1%*	12.5%
Range of motion	40.5%*	30.5%

*p<0.05

Based on owner evaluations at Day 7 and Day 14, improvement from initial visit was comparable for firocoxib and phenylbutazone. Table 4 summarizes the owner assessments of improvement. Both firocoxib and active control pastes were rated acceptable (97.6% and 95.2%, respectively) and convenient to administer (95.3% and 98.4%, respectively) by owners.

Table 4. Percentage of Horses Improved on Owner Assessment

Treatment	Percentage of Horses Showing Improvement	
	Day 7 (Visit 2)	Day 14 (Visit 3)
Firocoxib (n=122)	71.1%	73.8%
Phenylbutazone (n=118)	68.6%	74.4%

Mean hematology variables were within normal reference values for both treatment groups, although individual animals may have had values outside the reference range. There were no clinically significant changes noted. Within-treatment decreases from baseline in white blood cell (WBC) count and neutrophils were observed in the firocoxib-treated group. Within-treatment decreases in WBC count and neutrophils and increases in basophils were observed in the phenylbutazone-treated group.

In the firocoxib treated group, within-treatment increases in calcium were noted at V2, and decreases in glucose at V2 and V3. Mean calcium and glucose values were

within normal reference ranges, and no clinically significant effects were observed. In the phenylbutazone-treated group, within-treatment decreases in total globulin, glucose, and total protein, and increases in BUN and albumin/globulin ratio were noted at V2 and V3. Mean glucose, total protein, and BUN values were within normal reference ranges, though there were some horses with values outside reference ranges. No clinically significant changes were observed. The total globulin mean in the firocoxib treated group was slightly outside the reference range. No clinically significant changes were observed. The albumin/globulin ratio mean values were slightly below normal reference range. No clinically significant effects were observed.

- (e) **Statistical Analysis:** The primary effectiveness variable was subjective clinical improvement at study end (V3) as assessed by the Investigator. Comparison of treatments for incidence of clinical improvement was performed as a non-inferiority comparison with a one-sided lower 95% confidence limit. Improvement at study midpoint (V2) was also analyzed. Improvement was defined as (1) Reduction of at least one grade in lameness score, and/or (2) Combined reduction of at least 3 in scores for pain on manipulation/palpation, joint swelling (calculated and observed), and range of motion. Improvement was assigned a value of “0” if not improved and “1” if improved.

Secondary efficacy variables included clinical improvement, improvement in lameness score, pain on manipulation score, range of motion score and joint swelling scores as reported by the Investigator at V2, and Owner assessment of improvement on Days 7 and 14.

- (f) **Conclusions:** In field studies, firocoxib was shown to be safe and effective when administered at 0.1 mg/kg orally once daily for the control of pain and inflammation associated with osteoarthritis in horses. Owners found firocoxib oral paste both convenient to administer (95.3%) and acceptable (97.6%) to their horses.

- (g) **Adverse Reactions:** Adverse reactions were reported in both treatment groups during the studies. Adverse events are summarized in Table 5.

Table 5. Adverse Reactions Seen During U.S. Field Studies

Adverse Reactions	EQUIOXX n=127	Active Control n=125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose manure	1	0
Polydipsia	0	1
Urticaria	0	1

*Horses may have experienced more than one adverse reaction during the study.

3. TARGET ANIMAL SAFETY

Title: PR&D 0016801: A Study to Evaluate the Safety of Firocoxib (0.82% w/w) Administered to Horses in an Oral Paste Formulation at 1, 3, and 5X the Recommended Dose for Thirty Days

- (1) Type of Study: GLP Laboratory Study
- (2) Study Location: Merial-Missouri Research Center, Fulton, MO
- (3) General Design:
 - (a) Purpose: To determine the safety of firocoxib administered to horses orally once daily at 1, 3, and 5X the recommended dose of 0.1 mg/kg for 30 days.
 - (b) Test Animals: Thirty-six healthy horses (12 male castrates and 24 females, ranging in weight from 741 to 1228 lbs, and in age from 2 to 5 years) were randomly assigned to 6 treatment groups.
 - (c) Control: Control horses were sham-dosed.
 - (d) Dosage Form: Paste containing 0.82% firocoxib w/w in the final market formulation.
 - (e) Route of administration: Oral
 - (f) Dosage: See Table 1.

Table 1. Treatment Groups, PR&D 0016801

Treatment Groups	Dose, mg/kg	Number and Sex of Animals
1	0	2 male castrates and 4 females
2	0.1 mg/kg (1X) on Days 0-29, Necropsy on Day 30	2 male castrates and 4 females
3	0.3 mg/kg (3X) on Days 0-29, Necropsy on Day 30	2 male castrates and 4 females
4	0.5 mg/kg (5X) on Days 0-29, Necropsy on Day 30	2 male castrates and 4 females
5	0.3 mg/kg (3X) on Days 0-29, held for 60 days after last treatment, no necropsy	2 male castrates and 4 females
6	0.5 mg/kg (5X) on Days 0-29, held for 60 days after last treatment, no necropsy	2 male castrates and 4 females

- (g) Duration of Treatment: 30 days
 - (h) Variables measured: Physical examination, general and post-dosing observations, body weight, clinical chemistry, coagulation (APTT, Prothrombin time, and Thrombin Clotting Time), hematology, buccal mucosal bleeding time, plasma levels of firocoxib, urinalysis, and gross and microscopic evaluation.
 - (i) Statistical Analysis Methodology: A repeated measures analysis of covariance was used to analyze continuous variables.
- (4) Results: None of the horses died in this study or showed serious clinical signs of toxicity; however, clinically significant abnormalities (oral lesions in the 3X and 5X groups) were seen on physical examination and at necropsy. Oral lesions consisted of ulcers and erosions of the tongue, lips and gums.

Clinical pathology abnormalities were seen in the 5X group (lowered RBC, HCT and hemoglobin; lowered total protein, albumin, and globulin) but were most likely associated with parasitism.

- (5) Conclusions: Administration of the recommended dose of 0.1 mg firocoxib/kg body weight as an oral paste for 30 days was not associated with any adverse effects.

Title: PR&D 0083001: A Study to Evaluate the Safety of Firocoxib Administered to Horses in an Oral Paste Formulation at 1, 3, and 5X the Recommended Dose for Forty-two Days.

- (1) Type of Study: GLP Laboratory Study
- (2) Study Location: Merial-Missouri Research Center, Fulton, MO
- (3) General Design:
 - (a) Purpose: To determine the safety of firocoxib administered to horses orally once daily at 1, 3, and 5X the recommended dose of 0.1 mg/kg for 42 days.
 - (b) Test Animals: Thirty-two healthy horses (16 male castrates and 16 females, ranging in weight from 713 to 1230 lbs, and in age from 2 to 5 years) were randomly assigned to 4 treatment groups.
 - (c) Control: Control horses were sham-dosed.
 - (d) Dosage Form: Paste containing 0.82% firocoxib w/w in the final market formulation.

(e) Route of administration: Oral

(f) Dosage: See Table 2.

Table 2. Treatment Groups, PR&D 0083001

Treatment Groups	Dose, mg/kg	Number and Sex of Animals
1	0	4 male castrates and 4 females
2	0.1 mg/kg (1X)	4 male castrates and 4 females
3	0.3 mg/kg (3X)	4 male castrates and 4 females
4	0.5 mg/kg (5X)	4 male castrates and 4 females

(g) Duration of Treatment: 42 days

(h) Variables measured: Physical examination, general and post-dosing observations, body weight, clinical chemistry, coagulation (APTT, Prothrombin time, and Thrombin Clotting Time), hematology, buccal mucosal bleeding time, plasma levels of firocoxib, urinalysis, gastric endoscopy, and gross and microscopic evaluation.

(i) Statistical Analysis Methodology: A repeated measures analysis of covariance was used to analyze continuous variables.

(4) Results: All horses survived to the end of the study. On physical examination pre-study, horses in all study groups had a similar incidence of oral ulcers present on the inside of the lips, at the commissure of the mouth and on the buccal (cheek) mucosa. On Days 14 and 28 of the study, the control horses that had oral ulcers pre-study no longer had oral ulcers, yet ulcers persisted in all of the treated groups. In addition, the incidence and severity of oral ulcers increased in all of the treated groups (1X, 3X, 5X). On examination at the study end, there was an increase in the incidence of oral cavity (lip, gingiva, tongue) ulcers in the 3X and 5X horses. Microscopic findings for these groups paralleled the gross findings. In addition, statistically the incidence of lip ulcers observed grossly ($p=0.0756$) and microscopically ($p=0.0345$) increased as the dose increased.

Clinical chemistry and coagulation abnormalities were seen in several horses in the 5X group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study. This horse also had a concurrent prolonged bleeding time. At the study end this horse had 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 abnormal findings at the end of the study. After two weeks of treatment, one female in the 5X group had a prolonged bleeding time. At the study end she was also found to have bilateral tubulointerstitial nephropathy and bilateral papillary necrosis.

Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse with the prolonged bleeding time discussed above. The nephropathy had segmented cortical and medullary zones of dilated tubules accompanied by interstitial inflammation and edema. Papillary necrosis was present in one 1X male horse and the 5X female horse described above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

Analysis of plasma levels of firocoxib indicated that the drug was absorbed and systemically available at all doses. Plasma concentrations increased with dose, and were approximately dose proportional for the 1X and 3X dose groups. There was minimal or no increase in plasma concentration observed between the 3X and 5X, suggesting the presence of a saturable absorption process that can limit the magnitude of the absorbed (over)dose.

- (5) Conclusions: Firocoxib administered once daily at the recommended dose of 0.1 mg/kg body weight in a 0.82% oral paste formulation for 42 days causes oral ulceration and is associated with delayed healing of pre-existing oral ulcers. One horse treated at the recommended dose for 42 days had renal papillary necrosis.

Title: PR&D 0030701: A Safety Study to Evaluate the Toxicity of Firocoxib Oral Paste to Horses for Ninety-two Days

- (1) Type of Study: GLP Laboratory Study
- (2) Study Location: Meril-Missouri Research Center, Fulton, MO
- (3) General Design:
 - (a) Purpose: To evaluate the safety of firocoxib administered to horses orally once daily at 2.5X, 7.5X and 12.5X of the recommended dose of 0.1 mg firocoxib/kg body weight for 92 days.
 - (b) Test animals: Thirty horses (10 male castrates, 5 males and 15 females), ranging in age from 1 to 3 years, and weighing 690 to 1043 lbs were randomly assigned to 5 treatment groups. Group 5 was a recovery group to evaluate the reversibility of toxicity following approximately 92 days of treatment plus an additional 55-57 days without treatment.
 - (c) Control: Control horses were sham dosed.
 - (d) Dosage Form: Paste containing 2.05% firocoxib w/w in a formulation similar to, but not identical to, final market formulation.
 - (e) Route of administration: Oral

(f) Dosage: See Table 3.

Table 3. Treatment Groups, PR&D 0030701

Treatment Group	Dose, (mg/kg) 2.05 % w/w	Number and Sex of Animals	Duration of Treatment
1	0	3 Female (F) 1 Male (M) 2 Male Castrates (MC)	92 days
2	0.25 mg/kg (2.5X)	3 F, 1 M, 2 MC	92 days
3	0.75 mg/kg (7.5X)	3 F, 1 M, 2 MC	92 days
4	1.25 mg/kg (12.5X)	3 F, 1 M, 2 MC	92 days
5	1.25 mg/kg (12.5X)	3 F, 1 M, 2 MC	92 days (+55-57 days off dose)

(g) Treatment duration: 92 days

(h) Variables measured: Body weight, physical examination, post-dosing observations, plasma firocoxib levels, clinical chemistry, coagulation, hematology, urinalysis, oral and gastric endoscopy, and gross and microscopic evaluation.

(i) Statistical Analysis Methodology: A repeated measures analysis of covariance was used to analyze continuous variables.

(4) Results: There were no treatment-related deaths during the study; however, two horses died during the study. Ulcers of the lips, gingiva and tongue were seen in all treated groups (2.5X, 7.5X and 12.5X). The incidence of lip ulcers observed microscopically (inflammation, $p=0.0044$; erosions, $p=0.0006$; ulcers, $p=0.0229$, Cochran-Armitage trend test) increased as the dose increased. The incidence of tongue ulcers observed grossly ($p=0.0018$, Cochran-Armitage trend test) and microscopically (inflammation, $p=0.0109$; foreign body, $p=0.0198$; ulcers, $p=0.0109$, Cochran-Armitage trend test) increased as the dose increased.

Erosions of the skin of the mandible were seen grossly in all firocoxib-treated groups. The incidence of skin erosions observed microscopically (chronic active inflammation, $p=0.0554$, Cochran-Armitage trend test) increased as the dose increased.

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 12.5X groups. The incidence of kidney abnormalities observed grossly

($p=0.0149$, Cochran-Armitage trend test) and microscopically ($p=0.0189$, Cochran-Armitage trend test) increased as the dose increased.

Three 12.5X animals also had elevated GGT, SDH, ALT and AST values. Two of these three horses had nephropathy but no other abnormalities at the study end. Three horses in the 2.5X group and three horses in the 7.5X group had single erosions or ulcers in the glandular stomach; however, glandular stomach ulcers were not seen in the placebo or the 12.5X groups. One 2.5X horse had elevated urine GGT and urine protein on Day 28 of the study and at necropsy this horse had renal lesions consistent with NSAID toxicity and renal hemorrhage. Group 5 showed that the oral ulcers were partially reversible after 55-57 days off treatment, but the renal lesions were not.

Plasma firocoxib concentrations were approximately dose linear between the 2.5X and 7.5X dose groups, and somewhat lower than expected in the 12.5X group. There was no evidence of drug accumulation or significantly decreased drug bioavailability occurring at any time point between days 14, 28, 63, and 89/90.

- (5) Conclusions: Firocoxib administered once daily at 2.5X, 7.5X and 12.5X the recommended dose of 0.1 mg/kg using a 2.05% w/w paste formulation for 92 days confirmed the toxicity of firocoxib in horses. Treatment for approximately three months was associated with dose dependent increases in incidence and severity of oral ulcers, skin ulcers of the mandible, and nephropathy. Horses dosed at 12.5X for 92 days, then left untreated for an additional 55-57 days, showed partial to complete recovery from the oral and skin lesions, but renal lesions persisted.

4. HUMAN SAFETY

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human food safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the label as follows: "Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that EQUIOXX Oral Paste when used under the labeled conditions of use is safe and effective for the control of pain and inflammation

associated with osteoarthritis in horses.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and treat pain and inflammation associated with osteoarthritis in horses.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. New studies were conducted to support the effectiveness and safety of EQUIOXX Oral Paste in horses for the control of pain and inflammation associated with osteoarthritis in horses.

EQUIOXX Oral Paste is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
5,981,576	October 9, 2016
6,020,343	October 9, 2016

6. ATTACHMENTS:

Veterinary Package Insert
Client Information Sheet
Syringe Label
Carton Label