Date of Approval: August 20, 2010

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-313

EQUIOXX Injection

Firocoxib
Horses

For the control of pain and inflammation associated with osteoarthritis in horses

Sponsored by:

Merial Ltd.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-313

B. Sponsor: Merial Ltd.
3239 Satellite Blvd., Bldg. 500
Duluth, GA 30096-4640

Drug Labeler Code: 050604

C. Proprietary Name: EQUIOXX Injection

D. Established Name: Firocoxib

E. Pharmacological Category: Non-steroidal anti-inflammatory

F. Dosage Form: Non-aqueous injectable solution

G. Amount of Active Ingredient: 20 mg firocoxib per mL

H. How Supplied: 25 mL vial

I. How Dispensed: Rx

J. Dosage: One intravenous injection once daily for up to 5 days, at a dose of 0.04 mg/lb (0.09 mg/kg) body weight (BW).

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 be dependent on the response observed, but should not exceed 14 days.

K. Route of Administration: Intravenous injection (IV)

L. Species/Class: Horses

M. Indication: For the control of pain and inflammation associated with osteoarthritis in horses

II. EFFECTIVENESS:

A. Dosage Characterization:

1. PR&D 0124901: A Study to Demonstrate Comparable Systemic Drug Exposure between an Oral and Intravenous Formulation of ML-1,785,713 in Horses.

In this parallel study design, ten horses received a single dose of one of two treatments: firocoxib injection (2% w/v firocoxib) IV at a dose of 0.24 mg/kg body weight or firocoxib paste (EQUIOXX, 0.82% w/w paste formulation) orally (per os (PO)) at a dose of 0.3 mg/kg. Due to the limit of quantitation (LOQ) in the plasma analytical method, three times the actual dose for both the oral (0.1 mg/kg) and injection (0.08 mg/kg) were administered to ensure quantifiable plasma drug concentrations out to three half lives beyond the Cmax.

The area under the plasma concentration-time curve was calculated using the linear-logarithmic trapezoidal method from Time 0 to the last point at which drug concentration was quantified [AUC(0-LOQ)] and area under the curve extrapolated to infinity [AUC(0-INF)]. Cmax, Tmax, and terminal half-life (t1/2) were calculated. The results are listed in Table 1 below.

Table 1. Mean pharmacokinetics parameters (+/- Standard Deviation) for ML-1, 785,713 following administration of a single 0.24 mg/kg intravenous injection (Group 1) or a single 0.3 mg/kg oral dose (Group 2) to two groups of five adult horses in a parallel study design.

Parameter	**Group 1[a]**	**Group 2[b]**
Cmax, mcg/mL	0.69 (0.14)*	0.19 (0.03)*
Tmax, hour	0.017 (0.00)*	2.15 (2.18)*
$AUC_{0\text{-}LOQ,}$ hr·mcg/mL (unadjusted for dose)	4.49 (1.76)	5.42 (1.80)
$AUC_{0\text{-}inf,}$ hr·mcg/mL (unadjusted for dose)	4.91 (1.79)	5.93 (1.92)
$AUC_{0\text{-}inf}$[c], hr·mcg/mL (adjusted for dose)	1.47 (0.54)[NS]	1.42 (0.46) [NS]
Half-life, hr	29.50(10.50)[NSS]	35.90 (12.10)[NSS]
R_c[d]	2.3	2.7

[a]Group 1: 2% ML-1,785,713 in 50% v/v Glycerol Formal/50% v/v PEG 400.
[b]Group 2: 0.82% ML-1,785,713 Oral Paste.
[c]$AUC_{0\text{-}inf}$ adjusted to 0.1 mg/kg.
[d]Accumulation (R_c) = $1/(1-e^{-ke\cdot\tau})$ where τ = 24 hours and ke = 0.693/Half-life.
[NS]Not statistically significantly different, t-Stat = 0.16 with 8 df. P(T<=t) two-tail = 0.88.
[NSS]Not statistically significantly different, t-Stat = -0.89 with 8 df. P(T<=t) two-tail = 0.40
*observed peak concentration and time to peak concentration

The ratio of the mean AUC (0-LOQ) values (IV/PO) unadjusted for dose was 0.83; the ratio of the geometric mean AUC (0-LOQ) (IV/PO) values unadjusted for dose was 0.88. Calculations based on the IV/PO AUC ratio indicated that an IV dose of 0.09 mg/kg firocoxib injection would produce comparable plasma levels to the 0.1 mg/kg firocoxib oral paste in horses. Therefore, the 0.09 mg/kg IV dose was selected for use in the field.

2. 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.

This study (described in detail below under Section 3: Target Animal Safety) included a multiple-dose pharmacokinetics component demonstrating steady-state plasma firocoxib concentrations following IV and PO administration and determined dose linearity of steady-state trough plasma firocoxib concentrations over the dose range 1X to 5X. Table 2 summarizes trough plasma firocoxib concentrations by Hour (sampling time) and Dose Level. Dose-adjusted steady-state plasma firocoxib trough concentrations were not significantly different ($p < 0.05$) following IV and PO administration within each Dose Level over Hours 312, 768, and 984. Over all dose levels, the least square mean ratio for 984 hours-PO/768 hours- IV is 0.96 (90% CL: 0.90 to 1.03) and the least square mean ratio for 312 hours-PO/768 hours-IV is 0.94 (90% CL: 0.88 to 1.00). In addition, the results of this study demonstrate that steady-state plasma firocoxib trough concentrations, following IV or PO administration were linear but less than proportional in the dose range 1X to 5X (see Figure 1).

Table 2. Mean, median [Range] steady-state plasma firocoxib concentrations (mcg/mL) in horses following PO administration (312 hours), IV administration (768 hours), and PO administration (984 hours). N = eight horses (4M/4F) at each dose level.

	Dose Level		
	1X	**3X**	**5X**
Hour			
312	0.075 0.064 [0.036, 0.143]	0.175 0.143 [0.081, 0.373]	0.296 0.326 [0.102, 0.410]
768	0.072 0.067 [0.04, 0.128]	0.160 0.142 [0.046, 0.318]	0.267 0.297 [0.069, 0.383]
984	0.091 0.084 [0.029, 0.179]	0.170 0.158 [0.074, 0.282]	0.311 0.342 [0.093, 0.522]

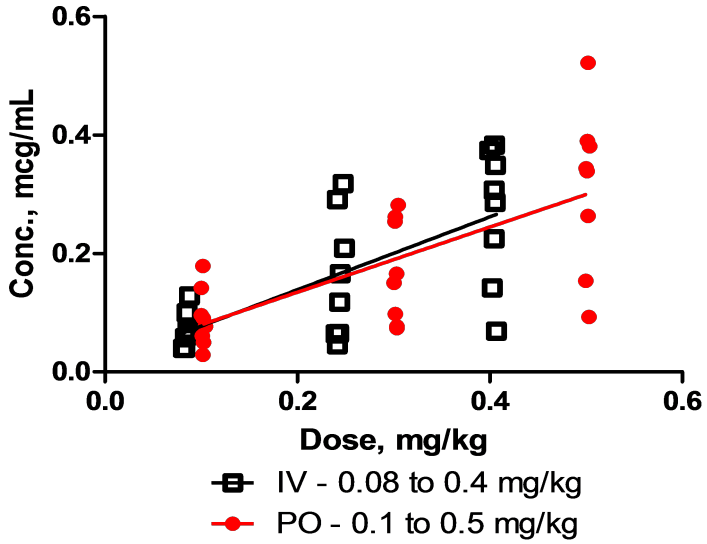

Figure 1. Observed steady-state trough plasma firocoxib concentrations in horses (N= 8 [4M/4F]/Dose Group) following IV dose on Study Day 31 (sampling time = 768 hours) and the PO dose on Study Day 40 (sampling time = 984 hours). Actual IV doses administered ranged from 0.08 mg/kg to 0.41 mg/kg; actual PO doses administered ranged from 0.10 mg/kg to 0.50 mg/kg. Linear regression analysis of each set of observations resulted in the same slopes statistically different from 0, 0.61 and 0.55 for the IV and PO doses, respectively, with the same intercepts (0.02, 0.02), r2= 0.045 and 0.48 for IV and PO, respectively.

B. Substantial Evidence:

1. Type of Study: 29-Day Bioequivalence Study

PR&D 0118201: A Study to Demonstrate Comparable Systemic Drug Exposure Between an Oral and Intravenous Formulation of ML-1,785,713 in Horses.

a. Investigators:

Study Director:
Dr. Bruce Kunkle
Merial Limited
Missouri Research Center

Principal Investigator, Bioanalytical Phase:
Ms. Valerie Kvaternick
Merial Limited
Pharmacokinetics and Drug Metabolism Department
North Brunswick, NJ

b. Study Design:

i. Purpose: To demonstrate comparable systemic drug exposure between a firocoxib injectable solution administered intravenously (IV) at a dose of 0.12 mg/lb (0.27 mg/kg) body weight and a paste formulation of ML-1,785,713 administered orally at a dose of 0.14 mg/lb (0.3 mg/kg) to horses. Due to the limit of detection of the bioanalytical method, 3X the actual dose for both the oral paste (0.045 mg/lb, 0.10 mg/kg) and injectable formulations (0.04 mg/lb, 0.09 mg/kg) were administered to ensure quantifiable plasma drug concentrations out to three half-lives beyond C_{max}.

ii. Study Animals: Twenty-six, healthy, grade male castrate horses between 2-15 years of age and 898-1,159 lbs (408-527 kg) were used.

iii. Treatment Groups:

Test Article (Treatment 1): The final market formulation of firocoxib (2 % w/v) injectable for horses was dosed at 0.12 mg/lb (0.27 mg/kg) intravenously once during each sequence.

Control (Treatment 2): EQUIOXX (0.82% w/w firocoxib) Oral Paste for horses (NADA 141-253) was dosed at 0.14 mg/lb (0.3 mg/kg) orally once during each sequence.

iv. Drug Administration: A two period cross over design with a 21-day washout period between treatments was used in this study. On Day -4, the horses were weighed for dosing calculations and ranked by decreasing body weight. The two heaviest horses formed Replicate 1 and the next two heaviest horses formed Replicate 2, etc., until 13 replicates were formed. Within replicates, horses were randomly allocated to one of the two treatment groups by drawing numbered pieces of paper from a hat.

	Day 0	Day 22
Sequence 1	Trt 1	Trt 2
Sequence 2	Trt 2	Trt 1

The horses were placed in assigned stalls at least 12 hours prior to treatment with only access to water. No food or bedding was accessible at that time. Animals were weighed on Day 21 for dosage

calculations for the second treatment period. Food has previously been demonstrated to have no impact on the extent of oral absorption of firocoxib.

v. Measurements and Observations: Blood samples were collected pre-dose on Day -4 and on Day 0 at approximately 1 and 5 minutes (Treatment 1 only), and at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 6, 8, 12, 24, 32, 48, 56, 72, 96, 120, 144, and 168 hours after treatment (for both treatment groups). Blood samples were collected on Day 21 pre-dose and Day 22 at approximately 1 and 5 minutes (Treatment 1 only), and at 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 6, 8, 12, 24, 32, 48, 56, 72, 96, 120, 144, and 168 hours after treatment (for both treatment groups).

Analysis of the plasma samples for determining firocoxib concentration was performed using a good laboratory practice (GLP)-validated, reversed-phase high performance liquid chromatography (HPLC) with ultraviolet (UV) detection method. The limit of quantitation, based on the sample volume of 2.0 or 1.0 mL, was either 7.5 or 25 ng/mL, respectively. The detection limit was either 5.0 or 12.5 ng/mL, respectively.

vi. Statistical Methods: Pharmacokinetic analyses were performed using WinNonlin software, version 5.0 (Pharsight Corporation, Mountain View, CA, 2002). Values were calculated for each animal and averaged for all animals under the same treatment. The area under the plasma concentration-time curve (AUC) was calculated using the linear/logarithmic trapezoidal method from 0 to the last point at which drug concentration was quantified [AUC(0-LOQ)] and 0 to infinity [AUC(0-inf)]. The terminal elimination half life (T½) was calculated via linear regression of the last linear quantifiable values. The z-test for means with known variance (Microsoft Excel 2003) was used to verify that there was no difference between the oral and IV half lives. Mean concentration values at 2 and 3 hours were evaluated using ANOVA (Microsoft Excel 2003) to verify concentrations after oral dosing and absorption were not significantly higher than after IV dosing. Cmax and Tmax for each animal were taken as the highest observed concentration and time to that observation. Bioequivalence parameters at the 90% confidence level were computed by the linear mixed effects module of WinNonlin.

c. Results: The bioequivalence study results are presented in Table 3.

Table 3. Summary of Average Pharmacokinetic Parameters Following a Single Dose of EQUIOXX (0.82% w/w firocoxib) Oral Paste at 0.14 mg/lb (0.30 mg/kg) (nominal) or an Intravenously-Administered Firocoxib Injectable Solution at 0.12 mg/lb (0.27 mg/kg) (nominal) to Horses.

	Oral paste Avg±SD (n=26)	IV Solution Avg±SD (n=26)
AUC(0-LOQ) (µg·hr/mL)	6.94±2.52	7.15±2.61
AUC(0-inf) (µg·hr/mL)	7.69±2.64	7.73±2.77
C_{max} (µg/mL)	0.177±0.033**	0.642±0.276**
T_{max} (hr)	2.02±2.32**	0.0195±0.0129**
***$T_{½el}$** (hr)	31.5±14.0	33.0±14.4

Avg=average (arithmetic) (rounded to 3 significant digits); SD=standard deviation;
AUC = Area Under the Curve; LOQ = last quantifiable time point; inf=infinity;
C_{max} = Peak Concentration; T_{max} = Time to Peak Concentration;
$T_{½el}$ = terminal elimination half life
*statistically no difference between half lives, p>0.05
** observed peak concentration and time to peak concentration

Following oral administration of the paste, the plasma level of firocoxib reached an average Cmax of 0.177 µg/mL with an average Tmax of 2.02 hours. By 144 hours post-dose, the plasma levels declined below the quantification limit in a majority of the animals.

After IV administration of the injectable formulation, the average observed peak plasma level of firocoxib (defined as the plasma drug concentration observed at the time of the first blood sample) was 0.642 µg/mL. By 144 hours post-dose the plasma concentrations in roughly half of the animals were below the quantification limit.

The concentration time profiles were parallel after the oral Tmax and the mean concentrations at the 2 and 3 hour sampling time points were not significantly different at the 0.05 significance level.

The terminal elimination half-life (T ½ el) values were not significantly different ($p>0.05$) with values ranging from 14.6 to 68.0 hours (mean = 31.5 hours) for the oral paste, and from 12.6 to 66.3 hours (mean = 33.0 hours) for the IV solution.

Bioequivalence was established for the injectable formulation based on AUC (O-LOQ). The average AUC ratio of the test (injectable) product at a dose of 0.27 mg/kg to the reference (oral) product at a dose of 0.3 mg/kg was 103%, and the lower and upper 90% confidence intervals were 99 and 106%, respectively.

d. Adverse Reactions: No treatment-related health observations were noted during this study and no concurrent medications were administered.

e. Conclusions: Based upon the equivalence of the comparability of systemic firocoxib exposure as defined by $AUC_{(O\text{-}LOQ)}$, firocoxib (2% w/v) injectable for horses, when administered at a dose of 0.041 mg/lb (0.09 mg/kg), will have a level of systemic exposure that is comparable to a 0.045 mg/lb (0.10 mg/kg) dose of EQUIOXX (0.82% w/w firocoxib) Oral Paste in horses.

2. Type of Study: Multi-center Field Study

Please refer to the FOI summary for EQUIOXX (0.82% w/w firocoxib) Oral Paste for horses (NADA 141-253), where a summary of the multi-center field study used as substantial evidence of effectiveness for approval can be found in Section "II. Effectiveness."

III. TARGET ANIMAL SAFETY:

A. GLP Study

1. 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 Horse

a. Study Location: Merial Limited, Missouri Research Center Fulton, MO, USA

b. Study Design: This study used a randomized complete block design.

i. Purpose: To determine the safety profile of an injectable solution of firocoxib when administered to horses intravenously once daily for 5 days at 0X, 1X, 3X, and 5X the recommended dose of 0.09 mg/kg, followed by once daily oral administration of firocoxib in a paste formulation for 9 subsequent days at 0X, 1X, 3X, and 5X the recommended dose of 0.1 mg/kg.

ii. Test Animals: 32 healthy horses (16 females and 16 males), 2-4 years of age, weighing 362-507 kg between 4 and 9 days prior to the start of treatment.

iii. Control: The control group received 0.9% sterile saline intravenously and sham-dosing for oral administration of the paste.

iv. Dosage Form: The treatment groups received EQUIOXX Injection (firocoxib 2% w/v Injection) and EQUIOXX Oral Paste (firocoxib 0.82% w/w oral paste).

v. Route of administration: Intravenous and oral administration.

vi. Dosage: Refer to Table 4.

Table 4. Treatment Groups, PR&D 0139501

Trt. Grp		Dose	Route	Treatment Days	Total No. Animals
1	0.9% sterile saline	0.2 mL/50kg (0X)	IV	0-4, 14-18, 28-32	8 4 female and 4 male
	Sham-dose	N/A (0X)	Oral	5-13, 19-27, 33-41	
2	2% w/v Firocoxib Injection	0.09 mg/kg (0.2 mL/50kg) (1X)	IV	0-4, 14-18, 28-32	8 4 female and 4 male
	Firocoxib (0.82% w/w) Oral Paste	0.1 mg/kg (1X)	Oral	5-13, 19-27, 33-41	
3	2% w/v Firocoxib Injection	0.27 mg/kg (0.6 mL/50kg) (3X)	IV	0-4, 14-18, 28-32	8 4 female and 4 male
	Firocoxib (0.82% w/w) Oral Paste	0.3 mg/kg (3X)	Oral	5-13, 19-27, 33-41	
4	2% w/v Firocoxib Injection	0.45 mg/kg (1.0 mL/50kg) (5X)	IV	0-4, 14-18, 28-32	8 4 female and 4 male
	Firocoxib (0.82% w/w) Oral Paste	0.5 mg/kg (5X)	Oral	5-13, 19-27, 33-41	

vii. Duration of Treatment: 42 days.

viii. Variables measured: Physical examination, general observations, body weight, local injection site reactions, clinical chemistry, coagulation, hematology, plasma concentrations of firocoxib, urinalysis, and gross and microscopic evaluation.

ix. Statistical Analysis Methodology: Analysis of covariance (ANCOVA), with baseline as the covariate was performed on temperature, respiration rate, and heart rate. Repeated measures ANCOVA was performed on variables with multiple data points (chemistry, coagulation, hematology, urine protein and specific gravity and body weight).

Frequency tables and Cochran-Mantel-Haenszel row means scores testing were used to summarize and analyze the injection site swelling data. Incidence of gross and microscopic abnormalities among treatment groups were compared using Fisher's Exact tests. All analyses utilized a two-sided significance level of α=0.10, except for any third order interactions which were tested at α =0.05.

c. Results: Two male 5X horses demonstrated a white focus in the renal cortex that correlated with mild to moderate tubulointerstitial nephropathy microscopically. While the presence of tubulointerstitial nephropathy was considered related to treatment, both horses were clinically healthy. White discoloration of the renal cortex was noted across all groups, including the control group. These gross lesions corresponded to various histological findings, including chronic interstitial nephritis (varying grades of chronic interstitial nephritis were noted in all 32 study horses); focal and multifocal lymphohistiocytic inflammation; and no corresponding microscopic abnormalities. These histological findings were not considered related to treatment.

One horse from the control group and two horses from the 5X group had injection site swellings during treatment. Perivascular inflammation was noted on microscopic evaluation in the two 5X horses but was not found in the 0X horse. Microscopic evaluation of the injection site revealed perivascular tissue changes in all study groups, including the saline-treated control group, characterized by an influx of inflammatory cells and rarely some tissue necrosis. While the perivascular lesions in the control and 1X dose group horses were similar, horses in the 3X dose group demonstrated increased lesion severity, and horses in the 5X group demonstrated increased lesion incidence and severity. The changes seen in the perivascular tissue were considered treatment-related.

At the time of necropsy, the following oral lesions were noted: buccal mucosal ulcers were only seen in the 5X group (3 horses); tongue ulcers/erosions were seen in the 1X group (2 horses), 3X group (1 horse), and 5X group (4 horses); gingival ulcers/erosions were seen in the control group (1 horse), 1X group (2 horses), 3X group (2 horses), and 5X group (5 horses). While lip ulcers and erosions were commonly seen across all study groups, increased lesion severity was noted in the 5X group at the time of necropsy. All other microscopic observations were considered to be incidental and unrelated to treatment. All horses survived to the end of the study and were clinically healthy at that time.

Across all study groups, there were individual and group fluctuations in various clinical chemistry endpoints during the treatment period. Liver

enzymes (SDH, GGT, AST) were noted to have a brief excursion out of reference range with a return to reference range by the next time point. These excursions were not associated with clinical signs or hepatic abnormalities at necropsy. One male 5X horse with an elevated GGT value on Day 42 of the study was noted to have renal tubulointerstitial nephropathy on necropsy. Similarly, coagulation parameters (PT, APT) were noted to have a brief excursion out of the reference range with return to reference range by the next time point. All mean values remained within reference range. No bleeding abnormalities were observed in any study animal.

A statistically significant treatment by sex effect was observed for body weight. The 5X group females had significantly lower mean body weights compared to the control group. This statistical finding was not considered clinically relevant.

Steady-state plasma firocoxib trough concentrations, following IV or PO administration, were linear but less proportional in the dose range 1X to 5X. In addition, steady-state plasma firocoxib trough concentrations were the same following IV and PO administration over the dose range 1X to 5X.

d. Conclusions: Firocoxib administered intravenously once daily for 5 days at 0X, 1X, 3X, and 5X the recommended dose of 0.09 mg/kg, followed by once daily oral administration of firocoxib for 9 subsequent days at 0X, 1X, 3X, and 5X the recommended dose of 0.1 mg/kg, for a total treatment of 42 days, was associated with a dose-dependent increase in the incidence of oral ulceration/erosion, perivascular inflammation at the injection site, and tubulointerstitial nephropathy. Firocoxib administration was also associated with a dose-dependent increase in the severity of oral ulceration/erosion and perivascular inflammation at the injection site.

IV. HUMAN FOOD 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, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

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

> 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.
>
> 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.

For technical assistance or to report suspected adverse events, call 1-877-217-3543.

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 and 21 CFR part 514. The data demonstrate that EQUIOXX Injection, 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:

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 the approval.

C. Patent Information:

EQUIOXX Injection is under the following U.S. patent numbers:

Patent Number	Expiration Date
5,981,576	July 21, 2018
6,020,343	October 9, 2016

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

VII. ATTACHMENTS:

Facsimile Labeling:

A. EQUIOXX Injection – Package Insert
B. EQUIOXX Injection – Client Information Sheet
C. EQUIOXX Injection-- Vial Label
D. EQUOIXX Injection-- Carton Label
E. EQUIOXX Injection—Small Shipping Label
F. EQUIOXX Injection—Large Shipping Label