Date of Approval: July 21, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-230

PREVICOX Chewable Tablets
(firocoxib)

For the control of pain and inflammation associated with osteoarthritis in dogs.

Sponsored by:

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

Table of Contents

1. GENERAL INFORMATION:

a. File Number:	NADA 141-230
b. Sponsor:	Merial Ltd. 3239 Satellite Blvd., Bldg. 500 Duluth, GA 30096-4640 Drug Labeler Code: 050604
c. Established Name:	Firocoxib
d. Proprietary Name:	PREVICOX
e. Dosage Form:	Scored chewable tablets
f. How Supplied:	The product is available as 57 or 227 mg round half-scored tablets in 60 count bottles and 10-count and 30-count blister packages.
g. How Dispensed:	Rx
h. Amount of Active Ingredient:	Each tablet contains 57 mg or 227 mg firocoxib.
i. Route of Administration:	Oral
j. Species/Class:	Dogs
k. Recommended Dosage:	PREVICOX should be administered orally at a dose of 2.27 mg/lb (5.0 mg/kg) body weight once daily. The tablets are scored and dosage should be calculated in half-tablet increments.
l. Pharmacologic Category:	Non-steroidal anti-inflammatory drug (NSAID)
m. Indications:	PREVICOX is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

2. EFFECTIVENESS:

a. Dosage Characterization:

A once daily oral dose of 5.0 mg/kg (2.27 mg/lb) body weight was selected based on the results of studies conducted in an experimental arthritis model.

In dose titration studies, dogs received a placebo control, 2.5, 5.0 or 7.5 mg/kg firocoxib orally ten hours prior to induction of arthritis. Force plate gait analysis and clinical assessments were performed prior to treatment, and 14 and 18 hours after treatment.

There was significant improvement in peak vertical force for all three firocoxib-treated groups when compared to placebo control group at 14 hours and 18 hours after treatment ($p < 0.01$). Peak vertical force after treatment with 5.0 mg/kg was 87.7% of full weight bearing baseline at 14 hours after treatment and 84.9% of baseline at 18 hours after treatment. The corresponding figures for the untreated control group were 0.0% at 14 hours and 33.0% at 18 hours. The dose response to firocoxib reached a plateau between 2.5 and 5.0 mg/kg, inclusive. Five mg/kg given once daily was selected as the dose for further study.

A second study was conducted in an experimental arthritis model with once daily oral administration of 5.0 mg/kg firocoxib. Force plate gait analysis and clinical assessments were performed prior to treatment, and at three and seven hours after treatment during the period of peak lameness.

There was statistically significant improvement in peak vertical force and clinical lameness scores for firocoxib-treated dogs when compared to placebo control group at both three and seven hours after treatment ($p \leq 0.05$). Peak vertical force after treatment with 5.0 mg/kg was 72.0% of full weight bearing baseline at three hours after treatment and 99.3% of baseline at seven hours after treatment. The corresponding figures for the placebo control group were 40.6% at three hours and 69.6% at seven hours. Clinical lameness scores for firocoxib-treated dogs also improved significantly as compared to placebo control group at both three and seven hours after treatment ($p \leq 0.05$). This study further supported the choice of 5.0 mg/kg firocoxib.

b. Substantial Evidence:

(1) Field Studies (PR&D 00535 and PR&D 00538)

Titles: PR&D 00535: A Study to Demonstrate the Efficacy, Safety and Acceptability of a ML-1,785,713 Oral Tablet in Dogs for the Control of Pain and Inflammation Associated with Osteoarthritis Under Field Conditions

PR&D 00538: A Study to Assess the Efficacy, Safety and Acceptability of ML-1,785-713 Oral Tablet in Dogs for the Control of Pain and Inflammation Associated with Osteoarthritis Under Field Conditions

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

(b) Investigators:

Investigators	Locations
Drs. Bert Shelley and Roger Sifferman	Springfield, MO
Dr. K.C. Brooks	Lodi, WI
Drs. Michael Conzemius and Wanda Gordon	Ames, IA
Drs. Jerry Case, Carla Case McCorvey and Melanie Bevere	Savannah, GA
Dr. James Schuessler	St. Louis, MO

(c) General Design:

1 Purpose: The objective of these studies was to demonstrate, under field use conditions, the effectiveness, safety and acceptability of firocoxib for the control of pain and inflammation associated with osteoarthritis in dogs.

2 Test Animals: Two hundred forty-nine dogs of various breeds were enrolled. The dogs ranged in age from 11 months to 20 years and weighed from 6.3 to 175 lbs. Two hundred forty dogs were used in the effectiveness evaluation.

3 Active Control: ETOGESIC (etodolac), 150 mg or 300 mg tablets

4 Diagnosis: Enrolled dogs were diagnosed with osteoarthritis via recent radiographic evidence of degenerative or bony changes. The dogs also had lameness scores of at least 2 (on a scale of 0 = no lameness to 4 = non-weight bearing lameness) at a walk or trot, or a combined score of at least 3 for lameness at a walk or trot, plus pain on palpation, swelling, or range of motion (on a scale for each variable of 0 = not present to 3 = severe).

5 Dose Form: Final market formulation of PREVICOX Chewable Tablets for Dogs, either 57 mg or 227 mg tablets.

6 Route of Administration: Oral

7 Dosages used: 5.0 mg/kg body weight of firocoxib, administered orally once daily; 10-15 mg/kg body weight of the active control, administered orally once daily.

8 Treatment Duration: 30 days

9 Variables Measured: For all dogs enrolled in the studies, physical examinations and lameness evaluations were conducted by the Investigator at the initial visit (Day –6 to Day 0), at the midpoint (approximately Day 14), and at the study's end (Day 29 +/- 3 days). Hematology and serum chemistry were evaluated prior to enrollment and at Day 29 +/- 3 days (only for dogs in PR&D 00535). The primary variable of effectiveness was the percentage of subjective improvement at the study end point. Improvement (treatment success) was defined as one of the following:

a. Reduction of at least 1 grade in lameness score at a walk or trot,

and/or

b. A combined reduction of at least 2 grades in scores for pain on palpation or manipulation, range of joint motion, and joint swelling

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

Overall Lameness Scoring (scored at a walk and a trot)
0 = No lameness
1 = Mild lameness (dog touched toe to floor on all strides)
2 = Moderate lameness (dog touched toe to floor on all strides)
3 = Severe lameness (dog touched toe to floor on at least 50% of strides)
4 = Non-weight bearing lameness (dog touched toe to floor on less than 50% of strides)

Pain on Palpation/Manipulation (most severely affected limb)
0 = No pain or not applicable
1 = Slightly painful (scarcely withdrew limb)
2 = Moderately painful (definitely withdrew limb)
3 = Severely painful (prominently withdrew limb)

Range of Motion (most severely affected limb)
0 = Normal range of motion
1 = Slightly reduced (less than 25% reduction in range)
2 = Moderately reduced (25% to 50% reduction in range)
3 = Severely reduced (greater than 50% reduction in range)

Joint Swelling (most severely affected limb)
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 fluctuant fluid distension)

Owners subjectively scored improvement from the initial visit on approximately Days 7, 14, 21 and 29. General health observations were also recorded daily by the owners. At the end of the study, owners assessed whether the tablet was convenient to administer, and if the tablet was palatable to the dog. Scoring of improvement was as follows:

Improvement
0 = Greatly improved from initial visit
1 = Moderately improved from initial visit
2 = Mildly improved from initial visit
3 = No improvement from initial visit

For the dogs enrolled in study PR&D 00535, peak vertical force during trotting was assessed by force plate gait analysis of the most severely affected limb at baseline (Day –2 to Day 0) and at study's end (approximately Day 29).

(d) Results:

Two hundred and forty nine dogs were enrolled in the studies. Two hundred forty dogs were evaluated for effectiveness. Safety data were collected on all dogs receiving treatment for any period.

Treatment with 5.0 mg/kg firocoxib orally once daily resulted in overall clinical improvement that was comparable to the active control at both study midpoint (Day 14) and endpoint (Day 29). Both treatment groups showed improvement from the initial visit. The results are summarized in Table 1.

Table 1. Veterinary Clinical and Non-Inferiority Evaluation

Group	**Percentage of Dogs with Overall Veterinary Clinical Improvement**	
Treatment	**Day 14 (Visit 2)**	**Day 29 (Visit 3)**
Firocoxib	80.2% (97/121*)	87.6% (106/121)
Active Control	78.8% (93/118)	83.1% (98/118)
Test Article-Active Control (Lower Confidence Bound)	1.4% (-7.4%)	3.8% (-3.9%)
Is non-inferiority demonstrated? (margin of difference is 15%)	Yes	Yes

*One case had missing data for Visit 2 since the examination was not performed within the time frame specified in the protocol.

Table 2 summarizes the percentage of dogs that showed improvement in the two components that formed the veterinary clinical evaluation. The first

component evaluated "lameness at a trot" and "lameness at a walk." In order for an animal to be classified as "improved" in the lameness component, it had to show a decrease of at least one grade on at least one of the two lameness variables. The second component of the clinical improvement evaluation evaluated "pain on palpation or manipulation," "range of motion," and "joint swelling." In order for an animal to be classified as "improved" in this component, it had to show an improvement of at least two grades in any of these three variables taken together. This could be demonstrated by either an improvement of two grades on one of the variables, or an improvement of one grade on two of the variables.

Table 2. Percentage of Dogs Showing Improvement in Veterinary Clinical Evaluation

	Percentage of Dogs that Showed Improvement	
Group	**Lameness at a walk and lameness at a trot**	**Pain on palpation, range of motion, and joint swelling**
Visit 2		
Firocoxib	76.0% (92/121*)	55.4% (67/121)
Active Control	76.3% (90/118)	43.2% (51/118)
Visit 3		
Firocoxib	82.0% (100/122*)	63.9% (78/122)
Active Control	78.8% (93/118)	47.5% (56/118)

*One case had missing data for Visit 2 since the examination was not performed within the time frame specified in the protocol.

Of the 249 dogs enrolled in the study, 172 dogs underwent force plate measurement of peak vertical force in gait. Of these, 164 dogs were included in the analysis. Eight dogs were excluded from the analysis for non-treatment-related reasons. Increased weight bearing on the affected limb, as measured by change in peak vertical force (Newtons/kilogram, N/kg) between the initial visit and study end, was comparable for firocoxib (0.15 N/kg; n = 87) and active control (0.20 N/kg; n = 80). The results are summarized in Table 3.

Table 3. Improvement in Peak Vertical Force on Day 29 (Visit 3)

Group	Percentage of Dogs with Improvement[1]
Firocoxib	14.1% (12/85)
Active Control	12.7% (10/79)
Test Article-Active Control (Lower Confidence Bound)	1.6% (-7.8%)
Is non-inferiority demonstrated? (Margin of difference is -15%)	Yes

[1]The criterion for classifying a dog as "improved" was an increase of at least 0.74 N/kg (Newtons/kg) in the dog's mean peak vertical force on Day 29 compared with its mean peak vertical force at baseline. The criterion was calculated as two times the pooled within-dog standard deviation of 0.37 N/kg.

Based on once weekly owner evaluations, improvement between firocoxib and the active control was comparable at all time points (Days 7, 14, 21, and 29). The scoring scale and values for each response at each evaluation are summarized in Table 4. Both firocoxib and the active control were rated palatable (68.5% and 53.7%, respectively) and convenient to administer (97.2% and 87.2%, respectively) by owners.

Table 4. **Results of Owner Evaluation of Improvement***

Time	Scoring	Firocoxib	Active Control
Day 7	0 = greatly improved	19.3% (23/119)	6.8% (8/116)
	1 = moderately improved	21.0% (25/119)	18.1% (21/116)
	2 = mildly improved	39.5% (47/119)	48.3% (56/116)
	3 = no improvement	20.2% (24/119)	26.7% (31/116)
Day 14	0 = greatly improved	20.8% (25/120)	8.5% (10/118)
	1 = moderately improved	33.3% (40/120)	31.4% (37/118)
	2 = mildly improved	31.7% (38/120)	38.1% (45/118)
	3 = no improvement	14.2% (17/120)	22.0% (26/118)
Day 21	0 = greatly improved	28.3% (34/120)	10.2% (12/118)
	1 = moderately improved	33.3% (40/120)	35.6% (42/118)
	2 = mildly improved	25.8% (31/120)	34.7% (41/118)
	3 = no improvement	12.5% (15/120)	19.5% (23/118)
Day 29	0 = greatly improved	32.8% (39/119)	16.9% (20/118)
	1 = moderately improved	31.1% (37/119)	32.2% (38/118)
	2 = mildly improved	23.5% (28/119)	28.8% (34/118)
	3 = no improvement	12.6% (15/119)	22.0% (26/118)

*Not all dogs were evaluated at each time point by the owners.

Minimal clinicopathologic changes were not treatment-related nor associated with clinical disease. The number of dogs with possible gastrointestinal (GI) tract-associated blood and protein loss was similar in both treatment groups (two firocoxib and three etodolac-treated dogs). These dogs had a minimum of three of the following findings: decreased red blood cell count, decreased hematocrit, increased or decreased mean corpuscular volume, decreased albumin, decreased globulins, and decreased total protein. One firocoxib-treated dog had a two-fold increase in neutrophils. One firocoxib-treated dog also had a two-fold increase in baseline BUN and creatinine (creatinine was 1.5 times normal reference range values). Hypocalcemia was noted in one firocoxib-treated dog and one etodolac-treated dog (Day 29 values were below normal reference range values for both dogs).

(e) Statistical Analysis:

The primary effectiveness variable was the incidence of veterinary clinical improvement at study end. 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 was also analyzed. Improvement was defined as: 1) Reduction of at least one grade in lameness score at a walk or a trot, and/or 2) Combined reduction of at least two grades in scores for pain on palpation or manipulation, range of motion, and joint swelling. Improvement was then assigned a value of "1" if improved or "0" if not improved.

Secondary effectiveness variables included veterinary scores for lameness at a walk or a trot, pain on palpation or manipulation, range of motion, and joint swelling, and the owner's assessment of improvement.

Analysis of peak vertical force was made based on the mean of valid observations on the designated limb. A dog was classified as "improved" if its peak vertical force increased from its baseline by at least two times the pooled within-dog standard deviation, obtained from repeated force plate trials. A non-inferiority evaluation was used to compare the incidence of improvement of firocoxib-treated dogs with active control-treated dogs, using a margin of –15%, as previously described for the overall clinical evaluation of improvement. The incidence of overall clinical improvement with firocoxib was within the margin of difference established for the non-inferiority comparison with the active control.

(f) Conclusions:

In field studies, firocoxib was shown to be safe and effective when administered at 5.0 mg/kg orally once daily for the control of pain and inflammation associated with osteoarthritis in dogs. Owners found chewable firocoxib tablets both convenient to administer (97.2%) and palatable (68.5%) to their dogs.

(g) Adverse Reactions:

Adverse reactions were reported in both treatment groups during the studies. Vomiting and decreased food consumption were the most common clinical adverse events seen in both the firocoxib and active control groups.

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

Adverse Reactions*	Firocoxib n=128**	Active Control n=121**
Vomiting	5	8
Decreased food consumption/Anorexia	3	3
Pain	2	1
Diarrhea	1	10
Lethargy	1	3
Somnolence	1	1
Hyperactivity	1	0
Melena	0	3
Stomatitis	0	1
Icterus	0	1
Constipation	0	1
Drooling	0	1
Alopecia	0	1

*Dogs may have experienced more than one adverse event during the study.
**"n" represents the total number of dogs in the treatment group.

3. ***TARGET ANIMAL SAFETY***

a. PR&D 0078601: A Study to Evaluate the Safety of Firocoxib Administered to Dogs in an Oral Chewable Tablet Formulation at 1, 3, and 5X the Recommended Dose

(1) Type of Study: Laboratory Study

(2) Investigator: Marlene D. Drag, DVM, MS, DACLAM
Merial-Missouri Research Center
Fulton, MO

(3) General Design:

(a) Purpose: To determine the safety of firocoxib administered to dogs orally once daily at 1, 3, and 5X the recommended dose of 5 mg/kg for six months.

(b) Test Animals: Thirty-two Beagle dogs (16 male and 16 female, ranging in weight from 7.70 to 14.75 kg, and in age from 7 to 10.9 months) were randomly assigned to four treatment groups (eight dogs per group).

(c) Control: Control dogs were not medicated.

(d) Dose Form: Scored tablets containing either 57 mg or 227 mg of firocoxib in the final market formulation

(e) Route of administration: Oral

(f) Dosage: Table 6 lists the treatment groups and the dose used for each:

Table 6. Treatment Groups

Treatment Groups	Dose, mg/kg	Number and Sex Of Animals
1	0	4 male and 4 female
2	5 mg/kg (1X)	4 male and 4 female
3	15 mg/kg (3X)	4 male and 4 female
4	25 mg/kg (5X)	4 male and 4 female

(g) Duration of Treatment: Six months
(h) Variables measured: Physical examination, general and post-dosing observations, food consumption, palatability, body weight, clinical chemistry, coagulation, hematology, plasma levels of firocoxib, urinalysis, gastric endoscopy, and gross (all animals) and histopathologic evaluation (controls and 5X animals)

(4) Results:

One dog in the 3X dose group was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, and proprioceptive deficits. Other clinical signs in this dog included elevated white blood cell counts, decreased and then increased platelet counts, decreased albumin levels, increased bleeding times, and elevated liver enzymes.

Decreased appetite/anorexia, vomiting, and diarrhea were seen in all dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group.

On histopathologic examination, a mild ileal ulcer and a focal hemorrhage in the heart was found in one 5X dog. This dog also had a transient elevation in white blood cell count and platelet count, and a transient decreased serum albumin, which returned to normal by study completion. One control and three 5X dogs had focal areas of inflammation in the pylorus or small intestine. Thalamic vacuolization was seen in two 5X group dogs, one 3X dog, and in two control dogs. The lesions were more severe in the 5X dogs. External thalamic capsular vacuolization was also seen in one control dog and in one 5X dog.

Sporadic incidences of increased white blood cell counts and decreased albumin were seen in all dose groups, including controls, but were seen at a greater frequency in the 3X and 5X groups. Mean ALP was within the normal reference range for all groups, but was statistically significantly greater in the 3X ($p = 0.0269$) and 5X ($p = 0.0816$) dose groups than in the control group.

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 proportional to dose over the dose range.

(5) Conclusions: This study demonstrated the safety of long-term administration of firocoxib in dogs over seven months of age. Dogs administered firocoxib once daily at the recommended dose for 180 days showed no clinically significant adverse events. At higher doses, transient hypoalbuminemia, leukocytosis, and elevations in ALP were reported. On histopathologic examination, a mild ileal ulcer was found in one 5X dog.

b. PR&D 0054101: A Safety Study to Evaluate the Toxicity of Firocoxib Oral Chewable Tablet Formulation Administered to Dogs at 1, 3, and 5X the Maximum Label Recommended Dose

(1) Type of Study: Laboratory Study

(2) Investigator: Sarah Nolan Smith, BSc, CBiol, MIBiol
Covance Laboratories Europe, Ltd.
North Yorkshire, HG3 1PY, United Kingdom

(3) General Design:
(a) Purpose: To determine the safety of firocoxib administered to dogs orally once daily at 1, 3, and 5X the recommended dose of 5 mg/kg for six months.
(b) Test animals: Thirty Beagle puppies (15 male and 15 female, ranging in age from 10-13 weeks at study start, and weighing 2.59-4.57 kg) were randomly assigned to five treatment groups (3 dogs per sex per treatment group). Table 7 lists the treatment groups, their doses, and the number of animals per group. Group E was intended to be a recovery group to examine the reversibility of lesions following 180 days of treatment and an additional 60 days without treatment.

Table 7. Treatment Groups

Treatment Group*	Dose (mg/kg)	Number and Sex of Animals
A	0	3 males and 3 females
B	5 mg/kg (1X)	3 males and 3 females
C	15 mg/kg (3X)	3 males and 3 females
D	25 mg/kg (5X)	3 males and 3 females
E	25 mg/kg (5X)	3 males and 3 females

(c) Control: Control puppies were not medicated.
(d) Dose Form: Scored chewable tablets containing 57 mg or 227 mg firocoxib (final market formulation)
(e) Route of administration: Oral
(f) Dosage: Each puppy's weight was multiplied by the desired dose multiple (for example 1 x bw, 3 x bw, 5 x bw where bw is the animal's body weight). Each dog was then dosed according to Table 8.

Table 8. Dosage Administration Table

CALCULATED WEIGHT MULTIPLE	TABLET SIZE/ ACTUAL DOSE
2.3-5.7 kg (5-12.5 lb)	½ tablet 57 mg (12.3-5 mg/kg)
5.8-11.3 kg (12.6-25 lb)	(1) 57 mg tablet (9.8-5 mg/kg)
11.4-22.7 kg (25.1-50 lb)	½ tablet 227 mg (9.9-5mg/kg)
22.8-45.4 kg (50.1-100 lb)	(1) 227 mg tablet (9.9-5 mg/kg)
Over 45.4 kg (over 100 lb)	Appropriate tablet combination

(g) Test duration: One hundred and eighty days (six months)
(h) Variables measured: Body weight, physical examination, post-dosing observations, plasma firocoxib levels, clinical chemistry and hematology, buccal mucosal bleeding times, urinalysis, gastric endoscopy, and gross and histopathologic evaluation

(4) Results: Four moribund puppies (one of six treated at 3X on Day 63, and three of twelve treated at 5X the indicated dose on Days 38, 78, and 79) were euthanized because of anorexia, weight loss, depression, and in one dog, vomiting. One puppy treated with firocoxib at 5X died on Day 82. The 3X puppy that was euthanized also had a decreased serum albumin. Two of the five animals that died or were euthanized had elevations in liver enzymes; these two animals were in the 5X dose group. One puppy had ingested a rope toy, which may have contributed to its demise.

When examined at necropsy and by histopathology, these five puppies all had moderate to severe periportal hepatic fatty change, two had duodenal ulceration, and two of the puppies also had pancreatic edema. One of these puppies had renal casts and one had renal hyaline droplets, although no corresponding lesions were seen on histopathology.

The remaining four 5X puppies from dose group D and two control puppies, all clinically normal, were euthanized to serve as comparisons to the ill animals. Two of these 5X puppies had periportal hepatic fatty change. One 5X puppy had focal nephropathy.

On average, the puppies in the 3X and 5X dose groups did not gain as much weight as controls. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs.

On day 83 of the study, dosing was discontinued for all puppies in both 5X dose groups. The four surviving puppies from 5X dose group E continued unmedicated for the remainder of the study (14 weeks). They had no significant lesions at necropsy at 180 days.

At 5 mg/kg, three out of six puppies had minimal periportal hepatic fatty change at necropsy, following 180 days of treatment. These animals showed no antemortem clinical signs or liver enzyme elevations. In the 3X dose group, three of the five surviving puppies had minimal periportal hepatic fatty change, one had pancreatitis, one had cystitis, and one had caecitis. Thalamic vacuolization was seen in three of six puppies in the 3X group and five of twelve puppies in the 5X groups. Diarrhea was seen in all dose groups.

(5) Conclusions: At 5 mg/kg, firocoxib treatment was associated with subclinical periportal hepatic fatty change in puppies less than seven months of age. At higher dose groups in this age dog, duodenal ulceration, hepatic fatty change, decreased weight gain, and decreased serum albumin were observed. One of twelve 5X puppies died and one of six 3X and three of twelve 5X puppies developed serious adverse reactions such as vomiting and depression, requiring euthanasia. The severity of the adverse reactions at the 3X and 5X doses, and the subclinical periportal hepatic fatty change in three of six puppies treated at the indicated dose, suggest that the drug may not be safe in young dogs. Furthermore, thalamic vacuolization was seen in three of six puppies in the 3X group and five of twelve puppies in the 5X groups. The clinical significance of this change is unknown.

c. PR&D 0053301: A Safety Study to Evaluate the Tolerance (10X) of Dogs to Firocoxib Chewable Tablet

(1) Type of Study: Laboratory Study

(2) Investigator: Marlene D. Drag, DVM, MS, DACLAM
Merial-Missouri Research Center
Fulton, MO

(3) General Design
(a) Purpose: To evaluate the safety of firocoxib in dogs at ten times the indicated dose for 22 days.
(b) Test Animals: Six Beagle dogs, three males and three females, ranging in age from 11-14 months old, weighing 10.6 to 13.25 kg body weight
(c) Control: Control animals were not medicated.

(d) Dose Form: Firocoxib in 57 mg and 227 mg scored tablet sizes (final market formulation)
(e) Route of Administration: Oral
(f) Dosage: The treatment groups, doses used, and numbers of animals per group are described in Table 9.

Table 9. Treatment Groups

Treatment Group	Dose mg/kg	Number and Sex of Animals
1	0	2 (1 male and 1 female)
2	10X (≥50 mg/kg)	4 (2 male and 2 female)

(g) Test Duration: Twenty-two days
(h) Variables measured: Body weight, food consumption, physical examination, post-dosing observations, hematology and clinical chemistry, buccal mucosal bleeding times, urinalysis, gastric endoscopy, and gross and histopathologic evaluation.

(4) Results: All dogs survived to the end of the study. Three of four treated dogs developed small intestinal erosion or ulceration. Treated dogs that developed small intestinal erosion or ulceration had a higher incidence of vomiting, diarrhea, and decreased food consumption/anorexia than control dogs.

One of these treated dogs developed a severe duodenal ulceration, with centrolobular hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, ketonuria, and elevations in AST and ALT. All four treated dogs exhibited progressively decreasing serum albumin that, with the exception of one dog that developed hypoalbuminemia, remained within normal range. Mild weight loss also occurred in the treated group. One control dog and three treated dogs exhibited transient increases in ALP that remained within normal range.

(5) Conclusions: Firocoxib administered at ten times the recommended dose (50 mg/kg) for 22 days resulted in small intestinal erosion or ulceration, decreased food consumption/anorexia, mild weight loss, sporadic vomiting and diarrhea, and decreased serum albumin in three of four treated animals. Increased in liver enzymes and ketonuria were observed in treated dogs. Hepatic fatty change was confirmed in one dog.

4. HUMAN FOOD SAFETY

This drug is intended for use in dogs 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: "Warnings: 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. **For use in dogs only.**"

5. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with 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 PREVICOX (firocoxib) Chewable Tablets, when used under the labeled conditions of use are safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

PREVICOX (firocoxib) Chewable Tablets are restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

U.S. Patent Number	Date of Expiration
5,981,576	October 9, 2016
6,541,646	October 8, 2019
6,677,373	October 8, 2019

6. ATTACHMENTS

Facsimile labeling is attached as indicated below:

a. Package insert for both 57 mg and 227 mg tablet sizes
b. Client Information Sheet for PREVICOX Chewable Tablets, 57 mg and 227 mg tablet sizes
c. Bottle label for 60 count bottle for both 57 mg and 227 mg tablet sizes
d. 30 count blister backing label for both 57 and 227 mg tablet sizes
e. Carton labels for 30 count blister packages for both 57 and 227 mg tablet sizes
f. 10 count blister backing label for both 57 and 227 mg tablet sizes
g. Carton labels for 10 count blister packages for both 57 and 227 mg tablet sizes
h. Display trays for 10 count and 30 count blister packages for both 57 and 227 mg tablet sizes
i. Shipping label for 60 count bottles of 57 and 227 mg tablet sizes
j. Shipping label for 30 count blister cartons of 57 and 227 mg tablet sizes
k. Shipping label for 10 count blister cartons of 57 and 227 mg tablet sizes