Date of Approval: December 18, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-230

PREVICOX

Firocoxib
Chewable Tablets
Dogs

Effect of Supplement: This supplement provides for the addition of a new indication for the control of postoperative pain and inflammation associated with soft-tissue surgery in dogs.

Sponsored by:

Merial Ltd.

TABLE OF CONTENTS

I. 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. Proprietary Name(s):	PREVICOX
D. Established Name(s):	Firocoxib
E. Pharmacological Category:	Non-steroidal anti-inflammatory drug (NSAID)
F. Dosage Form(s):	Single-scored chewable tablet
G. Amount of Active Ingredient(s):	Each tablet contains 57 or 227 mg firocoxib.
H. How Supplied:	The product is available as 57 and 227 mg round, single-scored tablets in 60-count bottles, and in 10-count and 30-count blister packages.
I. How Dispensed:	Rx
J. Dosage(s):	The recommended dosage of PREVICOX (firocoxib) for oral administration in dogs is 2.27 mg/lb (5.0 mg/kg) body weight once daily as needed for osteoarthritis and for 3 days as needed for postoperative pain and inflammation associated with soft-tissue surgery. The dogs can be treated with PREVICOX approximately two hours prior to surgery. The tablets are scored and dosage should be calculated in half tablet increments. PREVICOX Chewable Tablets can be administered with or without food.
K. Route(s) of Administration:	Oral
L. Species/Class(es):	Dogs
M. Indication(s):	PREVICOX (firocoxib) Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis and

for the control of postoperative pain and inflammation associated with soft-tissue surgery in dogs.

N. Effect(s) of Supplement: This supplement provides for the addition of a new indication for the control of postoperative pain and inflammation associated with soft-tissue surgery in dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage of 2.27 mg/lb (5.0 mg/kg) administered orally once-daily. The FOI Summary for the original approval of NADA 141-230 dated July 21, 2004, contains dosage characterization information for the 2.27 mg/lb (5.0 mg/kg) oral, once-daily dose of PREVICOX Chewable Tablets for the osteoarthritis indication.

B. Substantial Evidence:

1. Type of Study: Field Study

a. Title: "PR&D 0102101-0102111: A Study to Demonstrate the Efficacy and Safety of Firocoxib for Control of Post-Operative Pain and Inflammation in Dogs."

b. Investigators and Study Locations:

Dr. Michel Dubié Cabestany, France	Dr. Michel Dubor Lyon, France
Dr. Michel Gau Castres, France	Dr. Jean-François Marty Prades, France
Dr. Ingo Breymann Borken, Germany	Dr. Graziano Pengo Castelleone, Italy
Dr. K.C. Brooks Lodi, WI	Dr. James K. Schuessler Kirkwood, MO
Dr. Dean Rund Springfield, MO	Dr. Roger S. Sifferman Springfield, MO
Dr. Melissa Wiest O'Fallon, MO	

c. Study Design: This was a negative control, double-blinded, multi-center field study. Enrolled dogs underwent various abdominal (e.g. ovariohysterectomy, abdominal cryptorchidectomy, splenectomy, cystotomy) or major external surgeries (e.g. mastectomy, skin tumor removal $\geq$ 8 cm).

1) Objective: To demonstrate clinical effectiveness and safety of firocoxib when administered orally once daily at 5 mg/kg body weight, starting 2 hours (+/- 30 min.) prior to surgery and continuing for 2 additional days, to control postoperative pain and inflammation associated with soft-tissue surgery under field conditions.

2) Study Animals: Two hundred fifty-eight client-owned dogs of various breeds were enrolled in the field study. The dogs ranged in weight from 7.04 lbs (3.2 kg) to 167.64 lbs (76.2 kg) and in age from 10.5 weeks to 16 years. Of the 258 dogs enrolled, 146 were intact females, 39 were spayed females, 48 were intact males, and 25 were castrated males.

3) Treatment Groups: The dogs were randomly allocated to two treatment groups. All dogs received standard of care appropriate to the surgical procedure. However, dogs in Treatment Group 1 also received firocoxib at 2.27 mg/lb (5.0 mg/kg) orally once on Day 0 (approximately 2 hours prior to their surgical procedures) and then orally once daily through Day 2. Dogs in Treatment Group 2 (control group—sham-dosed [pilled]) received standard of care alone.

4) Drug Administration: Dogs in the firocoxib group received a dosage of 2.27 mg/lb (5.0 mg/kg) orally approximately 2 hours prior to surgery and then orally once daily through Day 2. Dogs in the control group were sham-dosed (pilled) orally approximately 2 hours prior to surgery and then orally once daily through Day 2.

5) Measurements and Observations:
The animals were assessed for pain using the Glasgow Composite Pain Scale (GCPS) and Visual Analog Scale (VAS) at the following time points: once between Days -3 and 0; Day 0—at approximately 90 minutes, 3, 5, 7, and 9 hours post-extubation; Day 1—at approximately 2 and 10 hours post-treatment; and Day 2—at approximately 2 hours post-treatment. The animals were rescued with non-NSAID analgesic medications if they scored ≥ 8 on the GCPS, or if the clinical investigator felt the dog in question was painful enough to warrant rescue without reaching a GCPS score of ≥ 8. Rescued animals were considered treatment failures.

All enrolled dogs received general health evaluations prior to surgery and in conjunction with the pain assessment time points. Physical examinations were conducted once between Days -3 and 0 and once daily on Days 1 and 2. Blood for hematology and blood chemistry analyses, and urine for urinalyses were obtained once pre-surgery and once on Day 2.

The GCPS is a pain assessment instrument which provides a composite score for clinicians to use in determining whether a dog is in pain and requires analgesic drug administration. The composite score is based on six categories including:

(I) Vocalization - Is the dog: quiet, crying or whimpering, groaning, or screaming?
(II) Attention to wound area - Is the dog: ignoring any wound or painful area, looking at the wound or painful area, rubbing the wound or painful area, or chewing the wound or painful area?
(III) Mobility - When the dog walks/rises is it: normal, lame, slow or reluctant, stiff, or refusing to move?
(IV) Response to touch – Does the dog: do nothing, look around, flinch, growl or guard the area, snap, or cry?
(V) Demeanor - Is the dog: happy and content or happy and bouncy, quiet, indifferent or non-responsive to surroundings, nervous or anxious or fearful, or depressed or non-responsive to stimulation?
(VI) Posture and Activity - Is the dog: comfortable, unsettled, restless, hunched or tense, or rigid?

The VAS is another pain assessment instrument. With this tool, the clinical investigators make marks which correspond to their patients' perceived pain on 100 mm horizontal lines. In this study, the following clinical signs were used to evaluate the dogs' pain: panting, restlessness, vocalization, looking at or licking at the wound excessively, biting, anxious appearance, reluctance to move, and/or inappetance.

6) Statistical Methods

The definition of effectiveness for this study was a success/failure variable based on the need for rescue medication. This variable was analyzed using a generalized linear mixed model with binomial error function and logit link function. The statistical model included treatment as a fixed effect, and site and site by treatment interaction as random effects.

The GCPS Total Score was analyzed using repeated measures analysis of variance. The statistical model included treatment, time, study site, and all interactions. Treatment, time, and the treatment by time interaction are fixed effects, whereas, study site and all interactions with study site are random effects. The last observation for GCPS was carried forward in case of missing observations due to treatment failure, early withdrawal for adverse events, or apparent lack of effectiveness.

d. Results

Two hundred fifty-four dogs were included in the effectiveness analysis. The treatments were statistically significantly different ($p = 0.006$ from the generalized mixed model) with respect to the success/failure variable used as the definition of effectiveness. Eight out of 126 (6.40%) firocoxib-treated

dogs and 31 out of 128 (24.2%) control dogs needed rescue medication, as shown in Table 1.

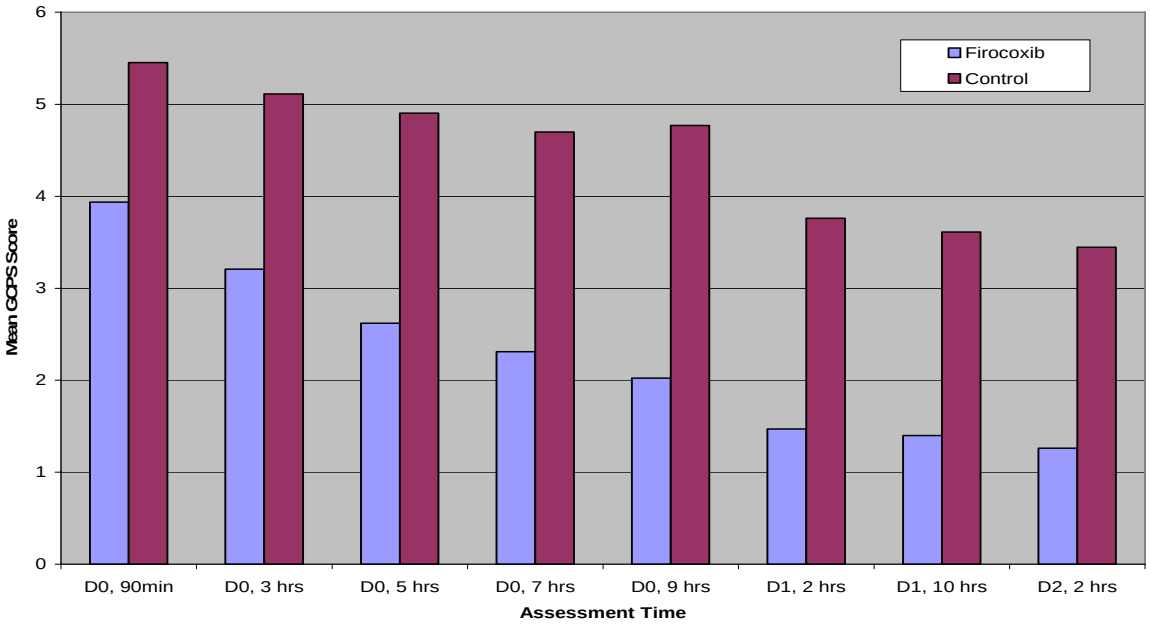
Table 1. Numbers of Dogs Needing Rescue Medication.

Treatment	Need for Rescue[a]		Total
	No	Yes	
Firocoxib	118 (93.6%)	8 (6.4%)	126
Control	97 (75.8%)	31 (24.2%)	128
Column Totals	215	39	254

[a] The difference in proportions of rescue was statistically significant ($p = 0.006$) using a generalized linear mixed model with logit link function.

The results from the repeated measures analysis of GCPS scores across time showed that the mean GCPS scores were consistently lower among dogs that received firocoxib in addition to standard of care compared to dogs that received standard of care alone (control group). This is shown in Figure 1. At each assessment point, the mean scores between the groups were statistically significantly different ($p < 0.05$). The mean VAS scores generally corresponded well to those of the GCPS, thus showing that dogs in the firocoxib group had lower scores (less pain) than the unmedicated control group.

Figure 1. Mean GCPS Scores by Treatment Group at Each Assessment Time Point.



Analyses of pre-surgery and Day 2 hematology, chemistry, and urine specific gravity data were performed. The results did not indicate clinically or biologically relevant changes for these variables in either the firocoxib-treated group or the control group.

e. Adverse Reactions: Eight dogs (6.3%) in the firocoxib group (n = 127) experienced at least one adverse reaction compared with 10 dogs (7.6%) in the control group (n = 131), as shown in Table 2. The most commonly-reported adverse reaction was emesis (3.9% in the firocoxib group, 4.6% in the control group). Note that dogs may have experienced more than one adverse reaction during the study.

Table 2. Adverse Reactions Reported in the Soft-tissue Surgery Field Study.

Adverse Reactions	**Firocoxib Group (n=127)**	**Control Group (Sham-dosed, pilled) (n=131)**
Vomiting	5 (3.94%)	6 (4.58%)
Diarrhea	1 (0.79%)	1 (0.76%)
Bruising at Surgery Site	1 (0.79%)	1 (0.76%)
Respiratory Arrest	1 (0.79%)	0 (0.0%)
SQ Crepitus in Rear Leg and Flank	1 (0.79%)	0 (0.0%)
Swollen Paw	1 (0.79%)	0 (0.0%)
Gastric Dilatation	0 (0.0%)	1 (0.76%)
Puffy Eyelids	0 (0.0%)	1 (0.76%)
SQ Hemorrhage Distal to Surgery Site	0 (0.0%)	1 (0.76%)
Suture Site Edema	0 (0.0%)	1 (0.76%)
Moderate Facial Edema	0 (0.0%)	1 (0.76%)
Decompensated	0 (0.0%)	1 (0.76%)

Dilated Cardiomyopathy		

f. Conclusions: Treatment with firocoxib at a dose of 2.27 mg/lb (5.0 mg/kg) body weight orally once daily starting at approximately 2 hours prior to surgery and continuing for two additional days was well-tolerated and was shown to statistically significantly reduce the number of dogs needing rescue medication when compared to an unmedicated, sham-dosed control ($p = 0.006$). GCPS scores indicated that at each time point, firocoxib-treated dogs experienced less pain than control dogs.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-230 dated July 21, 2004, contains a summary of target animal safety studies for use of PREVICOX Chewable Tablets in dogs at an oral, once-daily dose of 2.27 mg/lb (5.0 mg/kg).

IV. 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, 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 PREVICOX Chewable Tablets:

"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 oral use in dogs only."

The following items were examined to ensure human user safety: field data submitted in support of the original NADA, field data submitted in support of this supplemental NADA, field data submitted in support of the original NADA for EQUIOXX (firocoxib) Oral Paste for Horses (NADA 141-253), and the Material Safety Data Sheet (MSDS) for PREVICOX Chewable Tablets (dated August 31, 2004). No adverse events associated with human user safety occurred during any field studies conducted in support of the original and supplemental NADAs for PREVICOX Chewable Tablets, nor in the field studies conducted in support of the original NADA for EQUIOXX Oral Paste. The MSDS for PREVICOX Chewable Tablets provided by the sponsor indicates the drug product has no irritating effects on the skin or in the eyes, nor any potential for

sensitization to the drug. In the sponsor's experience, there are no harmful effects to humans when the product is used and handled according to specifications. Based on this information, PREVICOX Chewable Tablets have no human user safety issues other than those expected with inappropriate use or mishandling of the drug product.

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 PREVICOX Chewable Tablets, when used according to the label, are safe and effective for the control of postoperative pain and inflammation associated with soft-tissue surgery in dogs.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to provide adequate instructions for post-treatment care and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the new indication for the control of postoperative pain and inflammation associated with soft-tissue surgery for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

PREVICOX Chewable Tablets are under the following U.S. patent numbers:

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

VII. ATTACHMENTS:

Facsimile Labeling:

Carton Labels:
- 60 tablets—57 mg
- 60 tablets—227 mg
- 30 tablets—57 mg
- 30 tablets—227 mg
- 10 tablets—57 mg
- 10 tablets—227 mg

Bottle Labels:
- 60 tablets—57 mg
- 60 tablets—227 mg

Blister Labels:
- 10 tablets—57 mg
- 10 tablets—227 mg

Package Insert
Client Information Sheet