Date of Approval: September 23, 2008

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 orthopedic surgery in dogs.

Sponsored by:

Merial Ltd.

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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 and orthopedic surgery. The dogs can be treated with PREVICOX (firocoxib) approximately two hours prior to surgery. The tablets are scored and dose should be calculated in half tablet increments. PREVICOX Chewable Tablets can be administered with or without food. Use the lowest effective dose for the shortest period of time.
K. Route(s) of Administration:	Oral

L. Species/Class(es): Dogs

M. Indication(s): PREVICOX 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 and orthopedic 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 orthopedic 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 Freedom of Information (FOI) Summary for the original approval of NADA 141-230 dated July 21, 2004, contains the dosage characterization information for the 2.27 mg/lb (5.0 mg/kg) oral, once daily dose of PREVICOX Chewable Tablets as needed for the control of pain and inflammation associated with osteoarthritis.

B. Substantial Evidence:

1. Type of Study: Field Study

a. Title: "A Study to Demonstrate the Efficacy and Safety of Firocoxib for Control of Postoperative Pain and Inflammation in Dogs."

b. Investigators and Study Locations:

Dr. Kinsey L. Phillips Commerce, GA	Dr. Joachim Lopes de Lima Lattes-Montpellier, France
Dr. Roger S. Sifferman Springfield, MO	Dr. Ulrich Rytz Bern, Switzerland
Dr. C. H. Tangner Oklahoma City, OK	Dr. Ray Rudd Peachtree City, GA
Dr. Nicolas Diss Thionville, France	Dr. Enrico Stefanelli Roma, Italy
Dr. James K. Schuessler Kirkwood, MO	Dr. Janine Guaguère Lomme, France
Dr. Sabine Tacke	Dr. Bertrand Pucheu

Gießen, Germany	La Madeleine, France

c. Study Design: This was a double-blinded, multi-center field study in which PREVICOX was tested against a sham-dosed control. An add-on study design with rescue was used, where the effectiveness of firocoxib plus the standard of care was compared to a control group receiving the standard of care. All dogs could receive supplemental pain medication (rescue) at any time, as indicated. Enrolled dogs underwent an arthotomy and various surgical procedures to stabilize the joint including fabellar suture and/or imbrication, fibular head transposition, tibial plateau leveling osteotomy (TPLO) and "over the top" technique.

1) Objective: To demonstrate clinical effectiveness and field safety of firocoxib when administered orally once daily at 2.27 mg/lb (5 mg/kg) body weight, starting 2 hours (+/- 30 min) prior to surgery and continuing for 2 additional days, for the control of postoperative pain and inflammation associated with orthopedic surgery.

2) Study Animals: Out of 226 enrolled in the study that underwent surgery, 220 client-owned dogs were evaluated for effectiveness. Six dogs were not included for effectiveness due to protocol violations, dropouts, or missing data. Dogs ranged in age from 1 to 11.9 years in the PREVICOX-treated groups and 0.7 to 17 years in the control group.

3) Treatment Groups: The dogs were randomly allocated to two treatment groups. All dogs received standard of care appropriate to the surgical procedure. Anesthetic protocols included morphine administrations at approximately 0.11 mg/lb (approximately 0.25 mg/kg) prior to surgery and at extubation. Dogs in the PREVICOX group 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 the control group received the standard of care and sham-dosing.

4) Drug Administration: Dogs in the PREVICOX group received a dose 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 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 if they scored ≥ 8 on the GCPS, or if the clinical investigator felt the dog in question was painful enough to warrant rescue medication. Rescued dogs or dogs removed due to adverse events were considered treatment failures. These dogs were assessed for pain through the end of the study to ensure proper pain control.

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 validated pain assessment scale based on 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:

(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, licking 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?

Pain was also assessed using a VAS. The clinical investigators made marks which corresponded to the dogs' perceived pain on a 100 mm horizontal line. In this study, the following clinical signs were used to evaluate the dogs' pain: panting, restlessness, vocalization, looking at or licking at the wound, 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 successful completion of the study and 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 secondary effectiveness variables GCPS Total Score and VAS were analyzed using repeated measures analysis of variance beginning with the Day 0, 5 hour (± 30 minutes) time point; data from the time points prior were not included in the analysis. The statistical model for both variables included treatment, time, study site, and all interactions. Treatment, time, and the treatment by time interaction were fixed effects; study site and all interactions with study site were random effects. The last post-treatment (post-surgery) observations for GCPS Total Score and VAS were carried forward in case of missing observations due to treatment failure (rescue medication), protocol violators, early withdrawal for adverse events, or apparent lack of effectiveness.

d. Results

Two hundred twenty dogs (220) were included in the effectiveness database (116 PREVICOX cases). A total of 226 dogs were included in the field safety database (118 PREVICOX cases). The difference between treatments was significantly different ($p = 0.0050$) with respect to the success/failure variable used as the definition of effectiveness. Thirteen of the 116 (11.2%) PREVICOX-treated cases and 39 out of 104 (37.5%) control dogs were treatment failures, as shown in Table 1.

Table 1. Treatment Success in Firocoxib and Control Groups.

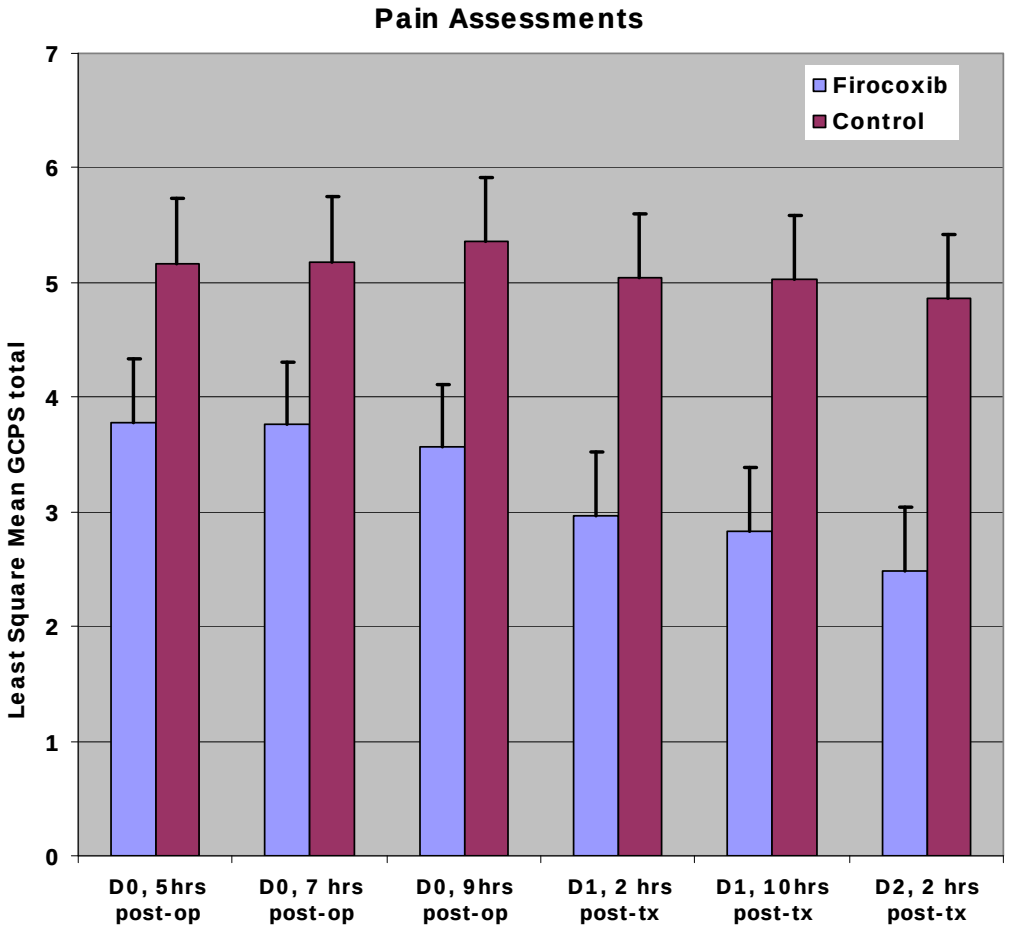
Treatment	Treatment Success[a]		Total
	Success	Failure	
Firocoxib[b]	103 (89.66%)	13 (11.2%)	116
Control	65 (62.14%)	39 (37.5%)	104
Total number of cases			220

[a] The difference in proportions of rescue was statistically significant ($p = 0.0050$) using a generalized linear mixed model with logit link function.
[b] One firocoxib case was a treatment failure due to adverse reactions.

Of the 220 dogs in the effectiveness database, 219 dogs were included in the secondary analysis of GCPS Total Score, VAS and individual GCPS category scores. The results from the repeated measures analysis of variance for GCPS total scores across time showed that the least squares means GCPS Total Scores were consistently lower ($p < 0.05$) 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.

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. There were six PREVICOX cases and one control case with normal pre- and elevated post-study BUN values.

e. **Adverse Reactions:** The most commonly-reported adverse reactions were diarrhea and bruising at the surgery site. The adverse reactions and the numbers of dogs experiencing each are summarized in Table 2. Some dogs experienced more than one adverse reaction during the study (e.g., vomiting multiple times).

Table 2. Adverse Reactions Reported in the Orthopedic Surgery Field Study.

Adverse Reactions	Firocoxib Group n=118	Control Group[a] n=108
vomiting	1	0
diarrhea	2[b]	1
bruising at surgery site	2	3
inappetance/decreased appetite	1	2
pyrexia	0	1
incision swelling, redness	9	5
oozing incision	2	0

A case may be represented in more than one category.
[a] Sham-dosed (pilled)
[b] one dog had hemorrhagic gastroenteritis

f. Conclusions: Treatment with PREVICOX 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. PREVICOX plus the standard of care was shown to be statistically significantly effective when compared to the sham-dosed control ($p = 0.0050$) receiving the standard of care. GCPS scores indicated that at each time point, PREVICOX-treated dogs had lower pain scores than the 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 in support 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:

"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".

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, when used according to the label, are safe and effective for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs.

A. Marketing Status:

The drug is restricted to use by or on the order of, a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the control of postoperative pain. Furthermore, the veterinarian monitors patients for possible adverse effects of the drug.

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 apply only to the new indication for the control of postoperative pain and inflammation associated with orthopedic 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 is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,981,576	July 21, 2018
6,541,646	October 8, 2019
6,677,373	October 8, 2019

VII. ATTACHMENTS:

Facsimile Labeling:
- Package Insert
- Owner Information Sheet
- 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

Display cartons:
57 mg
227 mg

cc: Document Control Unit, for the administrative file of:
N-141230-C-0032-B1, S-0033, S-0034, S-0036
Courtesy copy for the sponsor
HFV-12, FOI Staff
HFV-104, Green Book
HFA-305, Division of Dockets Management

Other administrative information: not applicable

template version- June 30, 2008

SIGNATURE PAGE FOR THE FREEDOM OF INFORMATION SUMMARY

NADA: 141-230
SUBMISSION NUMBER: C-0032
SPONSOR: Merial Ltd.
NAME OF DRUG: PREVICOX

	CONCURRENCE (DRAFT):		CONCURRENCE (FINAL):	
1.	_____		_____	
	Primary Reviewer Team 2, HFV-114	Date	INITIAL	Date
2.	_____		_____	
	Acting Leader Team 2, HFV-114	Date	INITIAL	Date
3.	_____		_____	
	Director Division of Therapeutic Drugs for Non-Food Animals HFV-110	Date	INITIAL	Date
4.	NA		_____	
	Director Division of Human Food Safety, HFV-150	Date	INITIAL	Date
5.	_____		_____	
	Quality Assurance Team, HFV-107	Date	INITIAL	Date
6.	_____		_____	
	Director ONADE, HFV-100	Date	INITIAL	Date
7.	_____		_____	
	Director CVM, HFV-1	Date	INITIAL	Date