HFA-305

Date of Approval: DEC 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.

2008-141-230

FOIS 2

TABLE OF CONTENTS

I. GENERAL INFORMATION: 1

II. EFFECTIVENESS: 2

A. Dosage Characterization: 2
B. Substantial Evidence: 2

III. TARGET ANIMAL SAFETY: 8

IV. HUMAN FOOD SAFETY: 8

V. USER SAFETY: 8

VI. AGENCY CONCLUSIONS: 8

A. Marketing Status: 9
B. Exclusivity: 9
C. Supplemental Applications: 9
D. Patent Information: 9

VII. ATTACHMENTS: 9

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 ≥ 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.

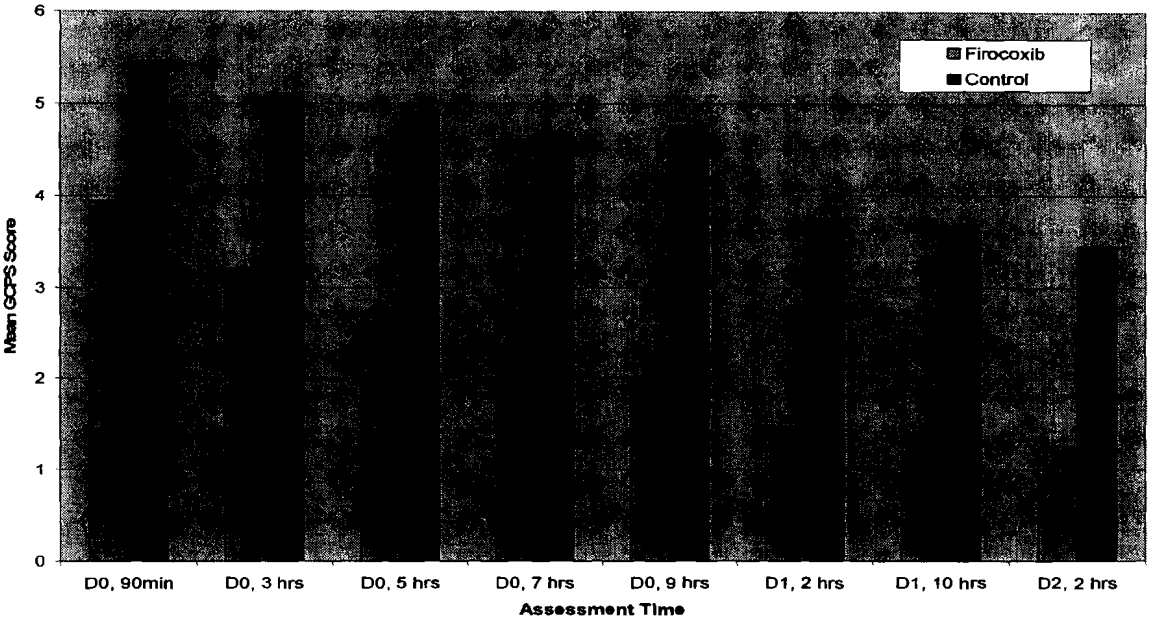
Table 1. Numbers of Dogs Needing Rescue Medication.

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 Dilated Cardiomyopathy	0 (0.0%)	1 (0.76%)

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

Product

Indications: 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.

Dosage and Administration: PREVICOX® should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily. Refer to package insert for full product information.

Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans. For use in dogs only.

Storage: Store at room temperature between 59°–86°F (15°–30°C). Brief periods up to 104°F (40°C) are permitted.

LOT & EXP

UNVARNISHED AREA

Rev. 10-2007
1030-2234-01

Merial Limited, a company limited by share, registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex CM19 5QA, England and domesticated in Delaware USA as Merial LLC

3 50604 27915 0

Product

Previcox®

(firocoxib)

Coxib-class non-steroidal anti-inflammatory drug

For Oral Use in Dogs Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 141-230, Approved by FDA

57 mg
60 Chewable Tablets

MERIAL

Manufactured for:
Merial Limited
3239 Satellite Blvd.
Duluth, GA 30096-4640.
U.S.A.
1-877-217-3543

© 2007 Merial Limited. All rights reserved. ®Previcox is a registered trademark of Merial Limited.

Previcox®
(firocoxib)
57 mg : 60 Chewable Tablets
Product

Product

Indications: 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.

Dosage and Administration: PREVICOX® should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily. Refer to package insert for full product information.

Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans. For use in dogs only.

Storage: Store at room temperature between 59°–86°F (15°–30°C). Brief periods up to 104°F (40°C) are permitted.

LOT & EXP

UNVARNISHED AREA

Rev. 10-2007
1030-2235-01

Merial Limited, a company limited by shares registered in England and Wales registered number 3332751 with a registered office at PO Box 327, Sandringham House Sandringham Avenue Harlow Business Park Harlow, Essex CM19 5QA England, and domesticated in Delaware USA as Merial LLC.

3 50604 27914 3

Product

Previcox®

(firocoxib)

Coxib-class non-steroidal anti-inflammatory drug

For Oral Use in Dogs Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 141-230,
Approved by FDA

227 mg
60 Chewable Tablets

Manufactured for:
Merial Limited
3239 Satellite Blvd.
Duluth, GA 30096-4640,
U.S.A.
1-877-217-3543

© 2007 Merial Limited. All rights reserved. ®Previcox is a registered trademark of Merial Limited.

Product

Previcox®
(firocoxib)
227 mg | 60 Chewable Tablets

Previcox®
(firocoxib)
Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only. Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA 141-230, Approved by FDA
57 mg | 30 Chewable Tablets
MERIAL
57 mg
30 Chewable Tablets
Previcox
Lot & Exp
PATHEON GMP CODE
3 50604 27912 9

MERIAL

227 mg 30 Chewable Tablets

Previcox

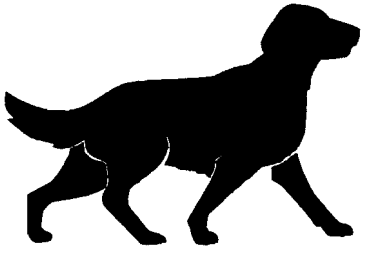
Previcox®

(firocoxib)

Coxib-class non-steroidal anti-inflammatory drug

For Oral Use in Dogs Only. ***Caution:*** *Federal law restricts this drug to use by or on the order of a licensed veterinarian.*

NADA 141-230. Approved by FDA.



227 mg | 30 Chewable Tablets

3 50604 27913 6

227 mg 30 Chewable Tablets

Previcox

PLACE PATHEON GMP CODE

57 mg
10 Chewable Tablets
Previcox
Previcox®
(firocoxib)
Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only. Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA 141-230, Approved by FDA
57 mg | 10 Chewable Tablets
MERIAL
PATHEON GMP CODE

MERIAL

227 mg 10 Chewable Tablets

Previcox

Product

Indications

Dosage and Administration

Warnings

Not for use in humans. Keep this and all medications out of the reach of children.

Consult a physician in case of accidental ingestion by humans. For use in dogs only.

Storage

Manufactured for

Previcox

227 mg 10 Chewable Tablets

Previcox

Lot & Exp

PLACE PATHEON GMP CODE

227 mg 10 Chewable Tablets

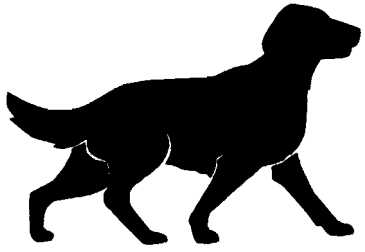
Previcox®

(firocoxib)

Coxib-class non-steroidal anti-inflammatory drug

For Oral Use in Dogs Only. ***Caution:*** *Federal law restricts this drug to use by or on the order of a licensed veterinarian.*

NADA 141-230, Approved by FDA

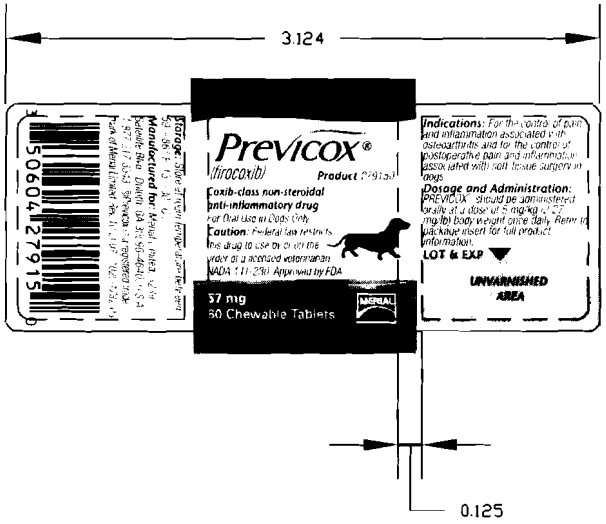


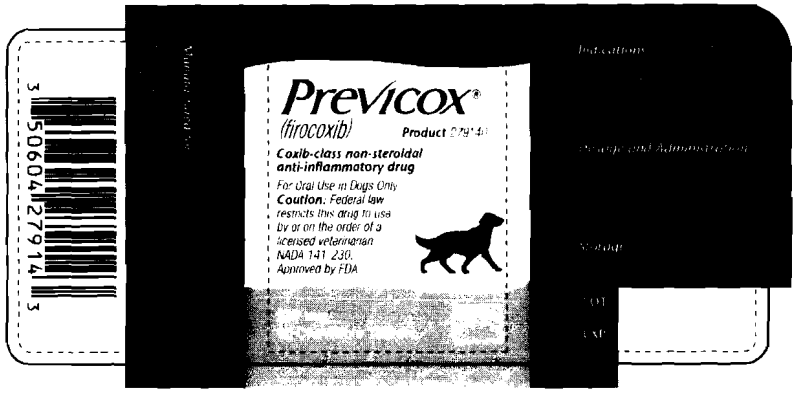
227 mg | 10 Chewable Tablets

3 50604 27917 4

227 mg 10 Chewable Tablets

Previcox


3.124
Previcox®
(firocoxib)
Product 27915
Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian
NADA 111-230 Approved by FDA
57 mg
60 Chewable Tablets
MERIAL
Indications: 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
Dosage and Administration: PREVICOX should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily. Refer to package insert for full product information.
LOT & EXP
UNVARNISHED AREA
0.125


Previcox®
(firocoxib)
Product
Coxib-class non-steroidal
anti-inflammatory drug
For Oral Use in Dogs Only
Caution. Federal law
restricts this drug to use
by or on the order of a
licensed veterinarian
NADA 141-230,
Approved by FDA
3 150604 279141 3

Previcox®

(firocoxib)

Chewable Tablets 57 mg

Not for use in humans. Keep this and all drugs out of the reach of children.
Consult a physician in case of accidental ingestion by humans.

For use in dogs only.

Store at room temperature between 59° and 86°F (15° – 30°C).

Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.

1077-1749-02
Rev. 11-2006

MERIAL

◀ LOT & EXP

Previcox®

(firocoxib)

Chewable Tablets 227 mg

Not for use in humans. Keep this and all drugs out of the reach of children.
Consult a physician in case of accidental ingestion by humans.

For use in dogs only.

Store at room temperature between 59° and 86°F (15° – 30°C).

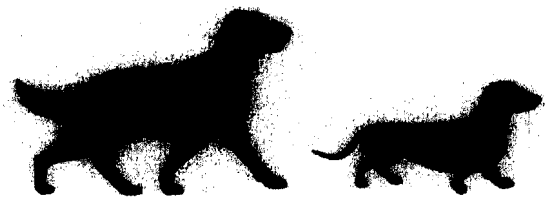
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.

LOT & EXP

1077-1751-03
Rev. 11-2006

MERIAL

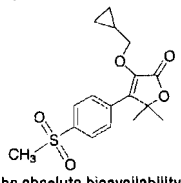
Previcox®
(firocoxib)



PREVICOX® (firocoxib) Chewable Tablets
For oral use in dogs only.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PREVICOX (firocoxib) belongs to the coxib class of non-narcotic, non-steroidal anti-inflammatory drugs. Firocoxib is a white crystalline compound described chemically as 3-(cyclopropylmethoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethylfuranone. The empirical formula is $C_{17}H_{20}O_5S$, and the molecular weight is 336.4. The structural formula is shown below:



Pharmacokinetics: The absolute bioavailability of PREVICOX (firocoxib) is approximately 38% when administered as a 5 mg/kg oral dose to fasted adult dogs. Firocoxib is rapidly cleared from the blood via hepatic metabolism and fecal excretion (CLsystemic = ~0.4 L/hr/kg). Despite a high level of plasma protein binding (96%), firocoxib exhibits a large volume of distribution (Vd_λ of total drug = ~4.6 L/kg) and a terminal elimination half life of 7.8 hours (%CV = 30%). The oral drug absorption process is highly variable among subjects. Co-administration of PREVICOX with food delays drug absorption (Tmax from 1 to 5 hours) and decreases peak concentrations (Cmax from 1.3 to 0.9 mcg/mL). However, food does not affect the overall oral bioavailability at the recommended dose.

Indications: PREVICOX (firocoxib) Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis and for the control of post operative pain and inflammation associated with soft-tissue surgery in dogs.

Dosage and Administration: Always provide the Client Information Sheet with prescription. Carefully consider the potential benefits and risks of PREVICOX and other treatment options before deciding to use PREVICOX. Use the lowest effective dose for the shortest duration consistent with individual response. 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.

Contraindications: Dogs with known hypersensitivity to firocoxib should not receive PREVICOX.

Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

For oral use in dogs only. Use of this product at doses above the recommended 2.27 mg/lb (5.0 mg/kg) in puppies less than seven months of age has been associated with serious adverse reactions, including death (see Animal Safety). Due to tablet sizes and scoring, dogs weighing less than 12.5 lb (5.7 kg) cannot be accurately dosed.

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum baseline data is recommended prior to and periodically during administration of any NSAID. ***Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given a Client Information Sheet about PREVICOX Chewable Tablets.***

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

Precautions: This product cannot be accurately dosed in dogs less than 12.5 pounds in body weight.

Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal, gastrointestinal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein bound drugs with PREVICOX Chewable Tablets has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications. The influence of concomitant drugs that may inhibit the metabolism of PREVICOX Chewable Tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

If additional pain medication is needed after the daily dose of PREVICOX, a non-NSAID class of analgesic may be necessary.

Appropriate monitoring procedures should be employed during all surgical procedures. Anesthetic drugs may affect renal perfusion, approach concomitant use of anesthetics and NSAIDs cautiously. The use of parenteral fluids during surgery should be considered to decrease potential renal complications when using NSAIDs perioperatively.

The safe use of PREVICOX Chewable Tablets in pregnant, lactating or breeding dogs has not been evaluated.

Adverse Reactions:

Osteoarthritis: In controlled field studies, 128 dogs (ages 11 months to 15 years) were evaluated for safety when given PREVICOX Chewable Tablets at a dose of 2.27 mg/lb (5.0 mg/kg) orally once daily for 30 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed adverse reactions during the study.

Adverse Reactions Seen in U.S. Field Studies

Adverse Reactions	*Previcox n=128*	*Active Control n=121*
Vomiting	5	8
Diarrhea	1	10
Decreased Appetite or Anorexia	3	3
Lethargy	1	3
Pain	2	1
Somnolence	1	1
Hyperactivity	1	0

PREVICOX (firocoxib) Chewable Tablets were safely used during field studies concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics.

Soft-tissue Surgery: In controlled field studies evaluating soft-tissue postoperative pain and inflammation, 258 dogs (ages 10.5 weeks to 16 years) were evaluated for safety when given PREVICOX Chewable Tablets at a dose of 2.27 mg/lb (5.0 mg/kg) orally approximately 2 hours prior to surgery and once daily thereafter for up to two days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed reactions during the study.

Adverse Reactions Seen in the Soft-tissue Surgery Postoperative Pain Field Study.

Adverse Reactions	*Firocoxib Group (n=127)*	*Control Group* (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%)

**Sham-dosed (pilled)*

Post Approval Experience: The following adverse reactions are based on voluntary post-approval reporting and are consistent with those reported for other cyclooxygenase inhibitory NSAID class drugs. The categories are listed in decreasing order of frequency by body system.

Gastrointestinal: Vomiting, anorexia, diarrhea, melena, hematemesis, hematochezia, weight loss, nausea, gastrointestinal ulceration, gastrointestinal perforation, salivation.

Urinary: Azotemia, elevated creatinine, polydipsia, polyuria, urinary tract infection, hematuria, urinary incontinence, renal failure.

Hematological: Anemia, thrombocytopenia.

Hepatic: Hepatic enzyme elevations, decreased or increased total protein and globulin, decreased albumin, decreased BUN, icterus, ascites, pancreatitis.

Neurological / Behavioral / Special Sense: Lethargy, weakness, seizure, ataxia, aggression, tremor, uveitis, mydriasis, nystagmus.

Cardiovascular / Respiratory: Tachypnea.

Dermatological / Immunological: Fever, facial / muzzle edema, pruritus, urticaria, moist dermatitis.

In rare situations, death has been reported as an outcome of the adverse events listed above.

Information For Dog Owners: PREVICOX, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include vomiting, diarrhea, decreased appetite, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue PREVICOX therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

Clinical Pharmacology: Mode of action: PREVICOX (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgesic properties. There are two main cyclooxygenase enzymes, COX-1 and COX-2, and a newly discovered third enzyme, COX-3, which has yet to be fully characterized.[1] Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiologic processes, e.g., platelet aggregation, gastric mucosal protection, and renal perfusion.[2] It also is constitutively expressed in the brain, spinal cord, and reproductive tract.[3] Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators, but it is also constitutively expressed in the brain, spinal cord and kidneys.[4, 5, 6] Cyclooxygenase-3 (COX-3) is also constitutively expressed in the canine and human brain and also the human heart.[7] Results from *in vitro* studies showed firocoxib to be highly selective for the COX-2 enzyme when canine blood was exposed to drug concentrations comparable to those observed following a once daily 5 mg/kg oral dose in dogs.[8] However, the clinical significance of these findings has not been established.

Effectiveness: Two hundred and forty-nine dogs of various breeds, ranging in age from 11 months to 20 years, and weighing 13 to 175 lbs, were randomly administered PREVICOX or an active control drug in two field studies. Dogs were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall improvement in a non-inferiority evaluation of PREVICOX compared with the active control. At the study's end, 87% of the owners rated PREVICOX-treated dogs as improved. Eighty-eight percent of dogs treated with PREVICOX were also judged improved by the veterinarians. Dogs treated with PREVICOX showed a level of improvement in veterinarian-assessed lameness, pain on palpation, range of motion, and owner-assessed improvement that was comparable to the active control. The level of improvement in PREVICOX-treated dogs in limb weight bearing on the force plate gait analysis assessment was comparable to the active control.

In a separate field study, two hundred fifty-eight client-owned dogs of various breeds, ranging in age from 10.5 weeks to 16 years and weighing from 7 to 168 lbs, were randomly administered PREVICOX or a control (sham-dosed-pilled) for the control of postoperative pain and inflammation associated with soft-tissue surgical procedures such as abdominal surgery (e.g. ovariohysterectomy, abdominal cryptorchidectomy, splenectomy, cystotomy) or major external surgeries (e.g. mastectomy, skin tumor removal ≥8 cm). The study demonstrated that PREVICOX treated dogs had significantly lower need for rescue medication than the control (sham-dosed-pilled) in controlling postoperative pain and inflammation associated with soft-surgery.

Palatability: PREVICOX Chewable Tablets were rated both convenient to administer (97.2%) and palatable to the dog (68.5%) by owners in multi-center field studies involving client-owned dogs of various breeds and sizes.

Animal Safety: In a target animal safety study, firocoxib was administered orally to healthy adult Beagle dogs (eight dogs per group) at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated dose of 5 mg/kg, there were no treatment related adverse events. Decreased appetite, vomiting, and diarrhea were seen in dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group. One dog in the 3X dose group was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting recurrent episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, proprioceptive deficits, decreased albumin levels, decreased and then elevated platelet counts, increased bleeding times, and elevated liver enzymes. On histopathologic examination, a mild ileal ulcer was found in one 5X dog. This dog also had a 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. Vacuolization without inflammatory cell infiltrates was noted in the thalamic region of the brain in three control, one 3X, and three 5X dogs. Mean ALP was within the normal range for all groups but was greater in the 3X and 5X dose groups than in the control group. Transient decreases in serum albumin were seen in multiple animals in the 3X and 5X dose groups, and in one control animal.

In a separate safety study, firocoxib was administered orally to healthy juvenile (10-13 weeks of age) Beagle dogs at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated (1X) dose of 5 mg/kg, on histopathologic examination, three out of six dogs had minimal periportal hepatic fatty change. On histopathologic examination, one control, one 1X, and two 5X dogs had diffuse slight hepatic fatty change. These animals showed no clinical signs and had no liver enzyme elevations. In the 3X dose group, one dog was euthanized because of poor clinical condition (Day 63). This dog also had a mildly decreased serum albumin. At study completion, out of five surviving and clinically normal 3X dogs, three had minimal periportal hepatic fatty change. Of twelve dogs in the 5X dose group, one died (Day 82) and three moribund dogs were euthanized (Days 38, 78, and 79) because of anorexia, poor weight gain, depression, and in one dog, vomiting. One of the euthanized dogs had ingested a rope toy. Two of these 5X dogs had mildly elevated liver enzymes. At necropsy all five of the dogs that died or were euthanized had moderate periportal or severe panzonal hepatic fatty change; two had duodenal ulceration; and two had pancreatic edema. Of two other clinically normal 5X dogs (out of four euthanized as comparators to the clinically affected dogs), one had slight and one had moderate periportal hepatic fatty change. Drug treatment was discontinued for four dogs in the 5X group. These dogs survived the remaining 14 weeks of the study. On average, the dogs in the 3X and 5X dose groups did not gain as much weight as control dogs. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs. Thalamic vacuolation was seen in three of six dogs in the 3X dose group, five of twelve dogs in the 5X dose group, and to a lesser degree in two unmedicated controls. Diarrhea was seen in all dose groups, including unmedicated controls.

In a separate dose tolerance safety study involving a total of six dogs (two control dogs and four treated dogs), firocoxib was administered to four healthy adult Beagle dogs at 50 mg/kg (ten times the recommended daily dose) for twenty-two days. All dogs survived to the end of the study. Three of the 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 than control dogs. One of these dogs had severe duodenal ulceration, with hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, ketonuria, and mild 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 of the two control dogs and three of the four treated dogs exhibited transient increases in ALP that remained within normal range.

Storage: Store at room temperature, between 59°–86° F (15°–30° C). Brief periods up to 104° F (40° C) are permitted.

To Request a Material Safety Data Sheet (MSDS), call 1-877-217-3543.

How Supplied: PREVICOX is available as round, beige to tan, half-scored tablets in two strengths, containing 57 mg or 227 mg firocoxib. Each tablet strength is supplied in 10 count and 30 count blister packages and 60 count bottles.

[1] Willoughby DA, Moore AR and Colville-Nash PR. COX-1, COX-2, and COX-3 and the future treatment of chronic inflammatory disease. *Lancet* 2000;355:646-648.

[2] Smith, *et al.*, Pharmacological Analysis of Cyclo-oxygenase-1 in Inflammation. *Proc. Natl. Acad. Sci. USA, Pharmacology* 1998;95:13313-13318.

[3] Jones CJ and Budsberg SC. Physiologic characteristics and clinical importance of the cyclooxygenase isoforms in dogs and cats. *JAVMA* 2000;217(5):721-729.

[4] Zhang, *et al.*, Inhibition of Cyco-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E_2 Production. *JPET* 1997;283:1069-1075.

[5] Jones and Budsberg, pp. 721-729.

[6] Zhang, et al., pp. 1069-1075.

[7] Chandrasekharan NV, Dai H, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure and expression. *Proc. Natl. Acad. Sci. USA*, 2002;99(21):13926-13931.

[8] Data on file.

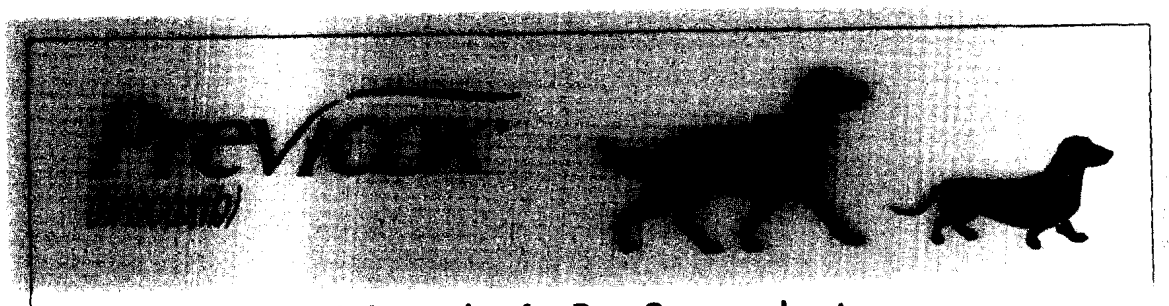
1050-1727-05
Rev. 11-2007

Manufactured for: Merial Limited
3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1-877-217-3543
U.S. Patent Nos. 5,981,576; 6,541,646; and 6,677,373
NADA 141-230, Approved by FDA

© 2007 Merial Limited. All Rights Reserved.
® PREVICOX is a registered trademark of Merial Limited.

MERIAL

6"W x 16"H FRONT



Information for Dog Owners about PREVICOX® (firocoxib) Chewable Tablets

PREVICOX Chewable Tablets are used for the control of pain and inflammation due to osteoarthritis or from soft-tissue surgery in your dog.

This summary contains important information about PREVICOX. You should read this information before you start giving your dog PREVICOX tablets and review it each time your prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want to know more about PREVICOX.

What is PREVICOX?

PREVICOX is a veterinary prescription non-steroidal anti-inflammatory drug (NSAID) used to control pain and inflammation due to osteoarthritis, or from soft-tissue surgery in dogs.

Osteoarthritis is a painful condition caused by "wear and tear" of cartilage and other parts of the joints that may result in the following changes or signs in your dog:

- Limping or lameness.
- Decreased activity or exercise (reluctance to stand, climb stairs, jump or run, or difficulty in performing these activities).
- Stiffness or decreased movement of joints.

Previcox is indicated for the control of postoperative pain and inflammation due to soft-tissue surgery (e.g., spays, abdominal surgeries, mastectomies, and removal of skin tumors). Your veterinarian may administer PREVICOX before the procedure and recommend that the dog be treated for several days after going home.

What kind of results can I expect when my dog is on PREVICOX for osteoarthritis?

While PREVICOX is not a cure for osteoarthritis, it can control the pain and inflammation and improve your dog's mobility.

- Response varies from dog to dog, but improvement can be quite dramatic.
- In most dogs, improvement can be seen within days.
- If PREVICOX is discontinued or not given as directed, your dog's pain and inflammation may return.

What kind of results can I expect when my dog is on PREVICOX for the control of pain and inflammation following soft-tissue surgery?

- PREVICOX Chewable Tablets allow your dog to recover more comfortably by controlling pain and inflammation following soft-tissue surgery.
- Control of pain and inflammation may vary from dog to dog.
- If PREVICOX Chewable Tablets are not given according to your veterinarian's directions, your dog's pain may return.
- Consult your veterinarian if your dog appears to be uncomfortable.

Which dogs should not take PREVICOX?

Your dog should not be given PREVICOX if he/she:

- Has an allergic reaction to firocoxib, the active ingredient in PREVICOX.
- Has had an allergic reaction (such as hives, facial swelling, or red or itchy skin) to aspirin or other NSAIDs.
- Is presently taking aspirin, other NSAIDs, or corticosteroids.
- Is under 12.5 pounds in body weight.

PREVICOX should only be given to dogs.

People should not take PREVICOX. Keep PREVICOX and all medications out of the reach of children. Call your physician immediately if you accidentally take PREVICOX.

What to tell/ask your veterinarian before giving PREVICOX.

Talk to your veterinarian about:

- The signs of osteoarthritis you have observed in your dog, such as limping or stiffness.
- The importance of weight control in the management of osteoarthritis.
- What tests might be done before PREVICOX is prescribed.
- How often your dog may need to be examined by your veterinarian.
- The risks and benefits of using PREVICOX. Serious adverse reactions, including death, have been associated with PREVICOX administration at doses above the recommended dose in puppies less than seven months of age.

Tell your veterinarian if your dog is currently experiencing or has ever had the following medical problems:

- Any side effects from taking PREVICOX or other NSAIDs, such as aspirin.
- Any digestive upset (vomiting and/or diarrhea).
- Any kidney disease.
- Any liver disease.

Tell your veterinarian about:

- Any other medical problems or allergies that your dog has now, or has had in the past.
- All medicines that you are giving or plan to give to your dog, including those you can get without a prescription and any dietary supplements.

Tell your veterinarian if your dog:

- Is under 7 months of age.
- Is pregnant, nursing or if you plan to breed your dog.

How to give PREVICOX to your dog.

PREVICOX should be given according to your veterinarian's instructions. Do not change the way you give PREVICOX to your dog without first speaking with your veterinarian. *Your veterinarian will tell you what amount of PREVICOX is right for your dog and for how long it should be given.* Most dogs will take PREVICOX Chewable Tablets from your hand, or you can place the tablet in your dog's mouth. PREVICOX may be given with or without food.

What are the possible side effects that may occur in my dog during PREVICOX therapy?

PREVICOX, like other NSAIDS, may cause some side effects. Serious side effects associated with NSAID therapy in dogs can occur with or without warning, and, in rare situations, result in death. *The most common side effects associated with PREVICOX therapy involve the digestive tract* (vomiting and decreased food consumption). Liver and kidney problems have also been reported with NSAIDs. Look for the following side effects that may indicate your dog is having a problem with PREVICOX:

- Decrease or increase in appetite.
- Vomiting.
- Change in bowel movements (such as diarrhea, or black, tarry or bloody stools).
- Change in behavior (such as decreased or increased activity level, incoordination, seizure, or aggression).
- Yellowing of gums, skin, or whites of the eyes (jaundice).
- Change in drinking habits (frequency or amount consumed).
- Change in urination habits (frequency, color, or smell).
- Change in skin (redness, scabs, or scratching).
- Unexpected weight loss.

It is important to stop the medication and contact your veterinarian immediately if you think your dog has a medical problem or side effect while taking PREVICOX tablets. If you have additional questions about possible side effects, talk with your veterinarian or call 1-877-217-3543.

Can PREVICOX be given with other medications?

PREVICOX should not be given with other NSAIDs (for example, aspirin, carprofen, etodolac, deracoxib, meloxicam, or tepoxalin) or corticosteroids (for example, prednisone, cortisone, dexamethasone, or triamcinolone).

Tell your veterinarian about all medications that you have given your dog in the past, and any medications you are planning to give with PREVICOX tablets. This should include other medicines that you can get without a prescription or any dietary supplements. Your veterinarian may want to check that all of your dog's medicines can be given together.

What do I do in case my dog eats more than the prescribed amount of PREVICOX?

Consult your veterinarian immediately if your dog eats more than the prescribed amount of PREVICOX.

What else should I know about PREVICOX?

- This sheet provides a summary of information about PREVICOX tablets. If you have any questions or concerns about PREVICOX, osteoarthritis pain, or postoperative pain following soft-tissue surgery, talk with your veterinarian.
- As with all prescribed medicines, PREVICOX tablets should only be given to the dog for which they were prescribed. They should be given to your dog only for the condition for which they were prescribed, at the prescribed dose.
- It is important to periodically discuss your dog's response to PREVICOX tablets. Your veterinarian will determine if your dog is responding as expected and if your dog should continue receiving PREVICOX tablets.

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

NADA 141-230, Approved by FDA
© 2007 Merial Limited. All Rights Reserved.
® PREVICOX is a registered trademark of Merial Limited.

1050-1727-05
Rev.11-2007

6"W x 16"H BACK