

Deramaxx® (deracoxib)

Chewable Tablets

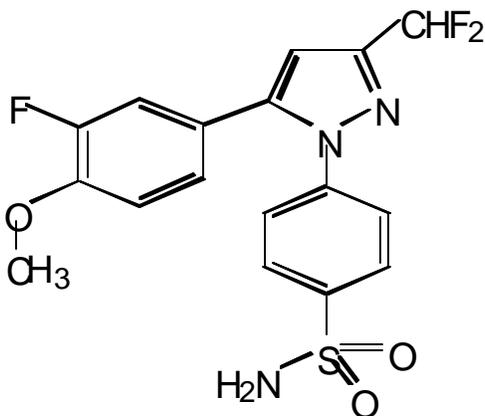
For Oral Use In Dogs Only

Caution:

Federal Law (U.S.) restricts this drug to use by or on the order of a licensed veterinarian.

Description:

DERAMAXX (deracoxib) is a non-narcotic, non-steroidal anti-inflammatory drug of the coxib class. DERAMAXX tablets are round, biconvex, chewable tablets that contain deracoxib formulated with beefy flavoring. The molecular weight of deracoxib is 397.38. The empirical formula is C17-H14-F3-N3-O3-S. Deracoxib is 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-1-yl] benzenesulfonamide, and can be termed a diaryl substituted pyrazole. The structural formula is:



Clinical Pharmacology

Mode of Action:

DERAMAXX tablets are a member of the coxib class of non-narcotic, non-steroidal, cyclooxygenase-inhibiting anti-inflammatory drugs for the control of postoperative pain and inflammation associated with orthopedic surgery and for the control of pain and inflammation associated with osteoarthritis in dogs.

Data indicate that deracoxib inhibits the production of PGE1 and 6keto PGF1 by its inhibitory effects on prostaglandin biosynthesis¹. Deracoxib inhibited COX-2 mediated PGE2 production in LPS-stimulated human whole blood².

Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiological processes (e.g., platelet aggregation, gastric mucosal protection, renal perfusion).³ Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators.⁴ Both COX isoforms are constitutively expressed in the canine kidney.⁵ At doses of 2-4 mg/kg/day, DERAMAXX tablets do not inhibit COX-1 based on *in vitro* studies using cloned canine cyclooxygenase⁶. The clinical relevance of this *in vitro* data has not been shown.

Although the plasma terminal elimination half-life for DERAMAXX tablets is approximately 3 hours, a longer duration of clinical effectiveness is observed.

Summary pharmacokinetics of DERAMAXX tablets are listed in Table 1.
Table 1: Pharmacokinetics of Deracoxib

Parameter	Value
Tmax ^a	2 hours
Oral Bioavailability (F) ^a	> 90% at 2 mg/kg
Terminal elimination half-life ^b	3 hours at 2-3 mg/kg 19 hours at 20 mg/kg
Systemic Clearance ^b	~ 5 ml/kg/min at 2 mg/kg ~1.7 ml/kg/min at 20 mg/kg
Volume of Distribution ^c	~ 1.5 L/kg
Protein binding ^d	> 90%

a Values obtained following a single 2.35 mg/kg dose

b Estimates following IV administration of deracoxib as an aqueous solution

c Based upon a dose of 2 mg/kg of deracoxib

d Based upon *in vitro* plasma concentrations of 0.1, 0.3, 1.0, 3.0, 10.0 µg/ml

Non-linear elimination kinetics are exhibited at doses above 8 mg/kg/day, at which competitive inhibition of constitutive COX-1 may occur.

Deracoxib is not excreted as parent drug in the urine. The major route of elimination of deracoxib is by hepatic biotransformation producing four major metabolites, two of which are characterized as products of oxidation and o-demethylation. The majority of deracoxib is excreted in feces as parent drug or metabolite.

Large intersubject variability was observed in drug metabolite profiles of urine and feces. No statistically significant differences between genders were observed.

Indications and Usage:

Osteoarthritis Pain and Inflammation:

DERAMAXX Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Dosage and Administration:

Osteoarthritis Pain and Inflammation: 0.45 – 0.91 mg/lb/day (1 to 2 mg/kg/day) as a single daily dose, as needed.

Postoperative Orthopedic Pain and Inflammation:

DERAMAXX Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs ≥ 4 lbs (1.8 kg).

Dosage and Administration:

Postoperative Orthopedic Pain and Inflammation: 1.4 – 1.8 mg/lb/day (3 to 4 mg/kg/day) as a single daily dose, as needed, **not to exceed 7 days of administration.**

Always provide “Information for Dog Owners” Sheet with prescription.

Since DERAMAXX tablet bioavailability is greatest when taken with food, postprandial administration is preferable. However, DERAMAXX tablets have been shown to be effective under both fed and fasted conditions; therefore, they may be administered in the fasted state if necessary. For postoperative orthopedic pain, administer DERAMAXX tablets prior to the procedure. Tablets are scored and dosage should be calculated in half-tablet increments. In clinical practice it is recommended to adjust the individual patient dose while continuing to monitor the dog’s status until a minimum effective dose has been reached.

Contraindications:

Dogs with known hypersensitivity to DERAMAXX or other NSAIDs should not receive DERAMAXX 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 use in dogs only.**

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID is recommended. **Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions, Animal Safety and Post-Approval Experience) and be given an “Information for Dog Owners” Sheet.**

Sensitivity to drug-associated adverse events varies with the individual patient. As a class, NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Patients at greatest risk for NSAID toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of DERAMAXX tablets with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided.

Precautions:

Plasma levels of deracoxib may increase in a greater than dose-proportional fashion above 8 mg/kg/day. DERAMAXX tablets have been safely used during field studies in conjunction with other common medications, including heartworm preventatives, anthelmintics, anesthetics, pre-anesthetic medications, and antibiotics. If additional pain medication is needed after a daily dose of DERAMAXX tablets, a non-NSAID/non-corticosteroid class

of analgesic may be necessary. It is not known whether dogs with a history of hypersensitivity to sulfonamide drugs will exhibit hypersensitivity to DERAMAXX tablets. The safe use of DERAMAXX tablets in dogs younger than 4 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated.

NSAIDs may inhibit the prostaglandins which 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. Appropriate monitoring procedures should be employed during all surgical procedures. The use of parenteral fluids during surgery should be considered to decrease potential renal complications when using NSAIDs perioperatively. Concurrent administration of potentially nephrotoxic drugs should be carefully approached.

The use of concomitantly protein-bound drugs with DERAMAXX 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 metabolism of DERAMAXX tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

Animal Safety:

In a 6-month study, dogs were dosed with DERAMAXX at 0, 2, 4, 6, 8 and 10 mg/kg with food once daily for 6 consecutive months. There were no abnormal feces, and no abnormal findings on clinical observations, food and water consumption, body weights, physical examinations, ophthalmoscopic evaluations, macroscopic pathological examinations, hematology, or buccal bleeding time. Urinalysis results showed hyposthenuria (specific gravity < 1.005) and polyuria in one male and one female in the 6 mg/kg group after 6 months of treatment. After 6 months of treatment, the mean BUN values for dogs treated with 6, 8, or 10 mg/kg/day were 30.0, 35.3, and 48.2 mg/dL respectively. No effects were seen on any other clinical chemistry parameters, including other variables associated with renal physiology (serum creatinine, serum electrolytes, and urine sediment evaluation). Dose dependent focal renal tubular degeneration/regeneration was seen in some dogs treated at 6, 8, and 10 mg/kg/day. Focal renal papillary necrosis was seen in 3 dogs dosed at 10 mg/kg/day and in one dog dosed at 8 mg/kg/day. No renal lesions were seen at the label doses of 2 and 4 mg/kg/day. There was no evidence of gastrointestinal, hepatic, or hematopoietic pathology at any of the doses tested.

In a laboratory study, healthy young dogs were dosed with deracoxib tablets once daily, within 30 minutes of feeding, at doses of 0, 4, 6, 8, and 10 mg/kg body weight for 21 consecutive days. No adverse drug events were reported. There were no abnormal findings reported for clinical observations, food and water consumption, body weights, physical examinations, ophthalmic evaluations, organ weights, macroscopic pathologic evaluation, hematology, urinalyses, or buccal mucosal bleeding time. In the clinical chemistry results there was a statistically significant (p<0.0009) dose-dependent trend toward increased levels of blood urea nitrogen (BUN). Mean BUN values remained within historical normal limits at the label dose. No effects on other clinical chemistry values associated with renal function were reported. There was no evidence of renal, gastrointestinal, hepatic or biliary lesions noted during gross necropsy. Renal histopathology revealed trace amounts of tubular degeneration/regeneration in all dose groups including placebo, but no clear dose relationship could be determined. There was no histopathologic evidence of gastrointestinal, hepatic or biliary lesions.

In another study, micronized deracoxib in gelatin capsules was administered once daily to healthy young dogs at doses of 10, 25, 50, and 100 mg/kg body weight for periods up to 14 consecutive days. Food was withheld prior to dosing. Non-linear elimination kinetics occurred at all doses. At doses of 25, 50, and 100 mg/kg, reduced body weight, vomiting, and melena occurred. Necropsy revealed gross gastrointestinal lesions in dogs from all dose groups. The frequency and severity of the lesions increased with escalating doses. At 10 mg/kg, moderate diffuse congestion of gut associated lymphoid tissues (GALT) and erosions/ulcers in the jejunum occurred. At 100 mg/kg, all dogs exhibited gastric ulcers and erosions/ulcerations of the small intestines. There were no hepatic or renal lesions reported at any dose in this study.

In a 13-week study, deracoxib in gelatin capsules was administered to

healthy dogs at doses of 0, 2, 4, and 8 mg/kg/day. No test-article related changes were identified in clinical observations, physical exams, or any of the other parameters measured. One dog in the 8 mg/kg dose group died from bacterial septicemia secondary to a renal abscess. The relationship between deracoxib administration and the renal abscess is not clear.

Palatability:

DERAMAXX tablets were evaluated for palatability in 100 client-owned dogs of a variety of breeds and sizes. Dogs received two doses of DERAMAXX tablets, one on each of two consecutive days. DERAMAXX tablets were accepted by 94% of dogs on the first day of dosing and by 92% of dogs on the second day of dosing.

Effectiveness:

DERAMAXX tablets were evaluated in masked, placebo-controlled multi-site field studies involving client-owned animals to determine effectiveness.

Postoperative Orthopedic Pain and Inflammation Field Study:

In this study, 207 dogs admitted to veterinary hospitals for repair of a cranial cruciate injury were randomly administered DERAMAXX tablets or a placebo. Drug administration started the evening before surgery and continued once daily for 6 days postoperatively. Effectiveness was evaluated in 119 dogs and safety was evaluated in 207 dogs. Statistically significant differences in favor of DERAMAXX tablets were found for lameness at walk and trot, and pain on palpation values at all post-surgical time points. The results of this field study demonstrate that DERAMAXX tablets, when administered daily for 7 days are effective for the control of postoperative pain and inflammation associated with orthopedic surgery.

Adverse Reactions:

A total of 207 dogs of forty three (43) different breeds, 1-15 years old, weighing 7-141 lbs were included in the field safety analysis. The following table shows the number of dogs displaying each clinical observation.

Abnormal Health Findings in The Postoperative Orthopedic Pain Field Study ¹		
Clinical Observation	DERAMAXX tablets N = 105	Placebo N= 102
Vomiting	11	6
Diarrhea	6	7
Hematochezia	4	0
Melena	0	1
Anorexia	0	4
Incision site lesion (drainage, oozing)	11	6
Non-incision Skin Lesions (moist dermatitis, pyoderma)	2	0
Otitis Externa	2	0
Positive joint culture	1	0
Phlebitis	1	0
Hematuria	2	0
Conjunctivitis	1	2
Splenomegaly	1	0
Hepatomegaly	1	0
Death	0	1

¹ Dogs may have experienced more than one of the observations during the study.

This table does not include one dog that was dosed at 16.92 mg/kg/day for the study duration. Beginning on the last day of treatment, this dog experienced vomiting, diarrhea, increased water intake and decreased appetite. Hematology and clinical chemistry values were unremarkable. The dog recovered uneventfully within 3 days of cessation of dosing.

Incisional drainage was most prevalent in dogs enrolled at a single study site. There were no statistically significant changes in the mean values for hepatic or renal clinical pathology indices between DERAMAXX tablet- and placebo-treated dogs. Four DERAMAXX tablet-treated dogs and two placebo-treated dogs exhibited elevated bilirubin during the dosing phase. One DERAMAXX tablet-treated dog exhibited elevated ALT, BUN and total bilirubin and a single vomiting event. None of the changes in clinical pathology values were considered clinically significant.

The results of this clinical study demonstrate that DERAMAXX tablets, when administered daily for 7 days to control postoperative orthopedic pain and inflammation in dogs, are well tolerated.

Osteoarthritis Pain and Inflammation Field Study:

Two hundred and nine (209) client-owned dogs with clinical and radiographic signs of osteoarthritis of at least one appendicular joint were enrolled in this study. A total of 194 dogs were included in the safety evaluation and a total of 181 dogs were included in the effectiveness evaluation. The effectiveness of DERAMAXX tablets in the control of pain and inflammation associated with osteoarthritis was demonstrated in a placebo-controlled, masked study evaluating the anti-inflammatory and analgesic effects of DERAMAXX tablets. Tablets were administered by the owner at approximately 1-2 mg/kg/day for forty-three (43) consecutive days.

In general, statistically significant ($p \leq 0.05$) differences in favor of DERAMAXX were seen for force plate parameters (vertical impulse area, peak vertical force) and owner evaluations (quality of life, lameness and overall level of activity).

The results of this field study demonstrate that DERAMAXX tablets, when administered at 1-2 mg/kg/day for 43 days, are effective for the control of pain and inflammation associated with osteoarthritis.

Adverse Reactions:

DERAMAXX was well tolerated and the incidence of clinical adverse reactions was comparable in DERAMAXX and placebo-treated animals. A total of 209 dogs of 41 breeds, 1-14 years old, weighing 17-177 lbs were included in the field safety analysis. The following table shows the number of dogs displaying each clinical observation.

Abnormal Health Findings in the Osteoarthritis Field Study¹		
Clinical Observation	DERAMAXX tablets n= 105	Placebo n= 104
Vomiting	3	4
Diarrhea/Soft Stool	3	2
Weight Loss	1	0
Abdominal Pain (splinting)	0	1
Seizure	1	0
Lethargy	0	1
Pyoderma/Dermatitis	2	0
Unilateral Conjunctivitis	1	0
Scleral Injection	0	1
Hematuria/UTI	1	0
Splenomegaly*	1	0
Grade II Murmur Systolic	1	0

¹ Dogs may have experienced more than one of the observations during the study.

* This dog was less active and eating less on enrollment, with elevated WBC, amylase, and AST and died 1 month after exiting the study. The dog was withdrawn from the study on Day 17 with anorexia, lethargy and a suspicion of diarrhea. Follow-up laboratory analyses revealed hypoalbuminemia, hyperphosphatemia, elevated AST and decreased BUN. Follow-up treatment included other anti-inflammatories and antibiotics.

Complete blood count, serum chemistry, and buccal bleeding time analysis were conducted at the beginning and end of the trial. Mean values of all CBC and chemistry results for both DERAMAXX and placebo-treated dogs were within normal limits. There was no statistically significant difference in the buccal bleeding time between DERAMAXX and placebo-treated dogs before or after the study, and all results remained within normal limits (less than 5 minutes). The results of this field study demonstrate that DERAMAXX is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

During this trial, dogs were safely treated with a variety of commonly used medications, including antibiotics, anti-parasitics, topical flea adulticides and thyroid supplements.

The results of this field study demonstrate that DERAMAXX tablets are well tolerated when administered at 1-2 mg/kg/day for up to 43 days for the control of pain and inflammation associated with osteoarthritis.

Post Approval Experience:

The following adverse reactions are based on voluntary post-approval reporting. The categories are listed in decreasing order of frequency by body system.

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

Hematological: Anemia, thrombocytopenia.

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

Neurological: Lethargy, weakness, seizure, ataxia, tremor, nystagmus, mydriasis.

Sensory: Vestibular signs, glazed eyes, uveitis.

Behavioral: Aggression, apprehension.

Urinary: Azotemia, polydipsia, polyuria, hematuria, low specific gravity, urinary incontinence, urinary tract infection, renal failure.

Cardiovascular: Bradycardia.

Respiratory: Tachypnea, coughing.

Dermatological/Immunological: Fever, edema, facial/muzzle edema, pruritis, urticaria, moist dermatitis, erythema, dermal ulceration/necrosis.

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

For technical assistance or to report suspected adverse events, call 1-800-332-2761.

Storage Conditions:

DERAMAXX tablets should be stored at room temperature between 59° and 86°F (15-30°C).

Keep this and all medications out of reach of children.

How Supplied:

DERAMAXX tablets are available as 25 mg and 100 mg round, brownish, half-scored tablets in 7, 30, and 90 count bottles.

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27408 USA

References:

1. Data on File
2. Data on File
3. Smith, et al.: "Pharmacological Analysis of Cyclo-oxygenase -1 in Inflammation," Proc. Natl. Acad. Sci. USA (October 1998) 95: 13313-13318, Pharmacology.
4. Zhang, et al.: "Inhibition of Cyclo-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E2 Production," *JPET*, (1997) 283: 1069-1075.
5. Verburg, KM et al. "Cox-2 Specific Inhibitors: Definition of a New Therapeutic Concept." *Amer J of Therapeutics* 8, 49-64, 2001.
6. Data on File

NADA # 141-203, Approved by FDA
© 2006 Novartis Animal Health US, Inc.
NAH/DXB-T/PI/3
01.06