

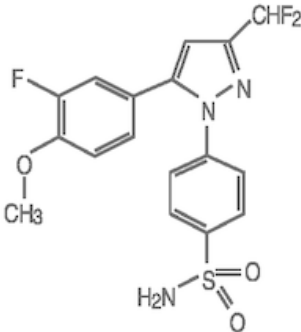


Caution:

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

Description:

DOXIDYL™ (deracoxib) is a non-narcotic, non-steroidal anti-inflammatory drug (NSAID) of the coxib class. DOXIDYL 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:

DOXIDYL 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 and dental surgery and for the control of pain and inflammation associated with osteoarthritis in dogs.

Data indicate that deracoxib inhibits the production of PGE1 and 6-keto PGF1 by its inhibitory effects on prostaglandin biosynthesis.¹ Deracoxib inhibited COX-2 mediated PGE2 production in LPS-stimulated human whole blood.²

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, deracoxib tablets do not inhibit COX-1 based on *in vitro* studies using cloned canine cyclooxygenase.⁶ The clinical relevance of this *in vitro* data has not been shown.

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

Summary pharmacokinetics of deracoxib 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 in 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:

Always provide “Information for Dog Owners” Sheet with prescription. Carefully consider the potential benefits and risk of DOXIDYL and other treatment options before deciding to use DOXIDYL. Use the lowest effective dose for the shortest duration consistent with individual response.

Osteoarthritis Pain and Inflammation:

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

Dosage and Administration:

Postoperative 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:

Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets. **Inaccurate dosing may result in adverse drug events (see Adverse Reactions, Animal Safety, and Post-Approval Experience).**

Postoperative Dental Pain and Inflammation:

DOXIDYL Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs.

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.

Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets. **Inaccurate dosing may result in adverse drug events (see Adverse Reactions, Animal Safety and Post-Approval Experience).**

Postoperative Dental Pain and Inflammation:

DOXIDYL Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with dental surgery in dogs.

Dosage and Administration:

Postoperative Dental Pain and Inflammation: 0.45 – 0.91 mg/lb/day (1 to 2 mg/kg/day) as a single daily dose, for 3 days. The first dose should be given approximately 1 hour prior to dental surgery and subsequent doses should be given daily for up to two additional treatments.

Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets. **Inaccurate dosing may result in adverse drug events (see Adverse Reactions, Animal Safety, and Post-Approval Experience).**

Since deracoxib chewable tablets bioavailability is greatest when taken with food, postprandial administration is preferable. However, deracoxib chewable 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 and dental pain, administer DOXIDYL 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 deracoxib should not receive DOXIDYL.

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. Do not use in cats.**

Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets. **Inaccurate dosing may result in adverse drug events (see Adverse Reactions, Animal Safety, and Post-Approval Experience).**

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.**

Precautions:

Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets. **Inaccurate dosing may result in adverse drug events (see Adverse Reactions, Animal Safety, and Post-Approval Experience).**

Since NSAIDs possess the potential to produce gastrointestinal ulceration and/or perforation, concomitant use of DOXIDYL tablets with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. As a class, NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. The following collective group of clinical signs has been reported with some serious gastrointestinal events, in decreasing order of reported frequency: anorexia, tachycardia, tachypnea, pyrexia, ascites, pale mucous membranes, dyspnea. In some cases, circulatory shock, collapse and cardiac arrest have also been reported. 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. Plasma levels of deracoxib may increase in a greater than dose-proportional fashion above 8 mg/kg/day. Deracoxib 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 DOXIDYL 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 DOXIDYL tablets. The safe use of deracoxib 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 deracoxib 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 deracoxib 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 deracoxib 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 pathological 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 severi-

ty 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.

Effectiveness:

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

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 deracoxib 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 deracoxib 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< 0.05) differences in favor of deracoxib 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 deracoxib 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:

Deracoxib was well tolerated and the incidence of clinical adverse reactions was comparable in deracoxib 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 adverse reaction.

Abnormal Health Findings in the Osteoarthritis Field Study ¹		
Clinical Observation	Deracoxib 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
Scieral injection	0	1
Hematuria/UTI	1	0
Splenomegaly*	1	0
Grade II murmur systolic	1	0

¹Dogs may have experienced more than one adverse reaction 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 deracoxib and placebo-treated dogs were within normal limits. There was no statistically significant difference in the buccal bleeding time between deracoxib 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 deracoxib 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-parasitides, topical flea adulticides and thyroid supplements.

The results of this field study demonstrate that deracoxib 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.



Doxidyl™
(deracoxib)

Chewable Tablets

For Oral Use

in Dogs Only

70168-11-0

