

Deramaxx™ (deracoxib) Flavor Tabs™

Non-steroidal Anti-inflammatory

DESCRIPTION:

DERAMAXX™ (deracoxib) is a non-steroidal anti-inflammatory drug belonging to the coxib class. Deracoxib is 4-[5-(3-difluoro-4-methoxyphenyl)-(difluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide, and can be termed a diaryl substituted pyrazole.

DERAMAXX™ Flavor Tabs™ tablets are round, biconvex and half-scored and contain deracoxib formulated together with beefy flavouring. Each tablet strength is formulated to be dosed on an animal weight basis for either acute or chronic pain.

INDICATIONS:

DERAMAXX Flavor Tabs are indicated for the relief of pain and inflammation associated with orthopedic surgery. DERAMAXX is also indicated for the treatment of chronic pain and lameness associated with osteoarthritis.

DERAMAXX is for use in dogs only.

PHARMACOLOGY:

Mode of Action

In pharmacologic studies, deracoxib has shown anti-inflammatory, analgesic, and antipyretic activity. Deracoxib reduces the pain and inflammation associated with orthopedic surgery or osteoarthritic disease by inhibition of prostaglandin synthesis, primarily via inhibition of the inducible isoenzyme of cyclooxygenase (cyclooxygenase-2, or COX-2). COX-2 is responsible for synthesis of inflammatory mediators of pain and inflammation. Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiological processes (e.g. platelet aggregation, gastric mucosal protection, and renal perfusion). Both COX isoforms are constitutively expressed in the canine kidney. At label doses, deracoxib does not inhibit COX-1, and is thus considered a COX-2 inhibitor. Deracoxib inhibited COX-2 mediated PGE₂ production in LPS-stimulated whole blood (dog, human). Higher doses were required to inhibit COX-1 mediated thromboxane production in whole blood (dog, human). This selectivity for COX-2 has been further demonstrated in a system using cloned canine COX-1 and COX-2. The clinical relevance of this *in vitro* information is not fully understood.

Pharmacokinetics

Parameter	Value (osteoarthritis dose)	Value (postoperative pain dose)
T _{max} (h)	1.5	2
C _{max} (µg/mL)	0.58	1.39
t _{1/2} (h)	~ 3	3.7
V _d (L/kg)	~ 1.5	~ 1.5
AUC ₀₋₂₄ (µg/mL)h	4.88	12.71

Deracoxib is rapidly absorbed orally. Deracoxib is > 90% bound to plasma proteins. 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 the parent drug and an o-demethylated metabolite.

DOSAGE AND ADMINISTRATION:

The daily dose of DERAMAXX Flavor Tabs is to be given as a single dose, with or without food. Tablets are scored and dosage should be calculated in half-tablet increments.

Postoperative pain and inflammation: 3 to 4 mg/kg/day as required, for a maximum of 7 days. If additional pain medication is needed in the first 24 hours post-operatively, a non-NSAID class of analgesic may be necessary. For additional information, please see under *Contraindications*. Dogs weighing less than 3.1 kg should not be administered Deramaxx for post-operative pain and inflammation.

Osteoarthritis pain and inflammation: 1 to 2 mg/kg/day. The individual patient dose should be adjusted to the minimum effective dose that achieves good clinical response. Dogs weighing less than 6.3 kg should not be administered Deramaxx for osteoarthritis pain and inflammation.

CONTRAINDICATIONS:

As with all non-steroidal anti-inflammatory drugs (NSAIDs), administration of this drug is advised against in the following circumstances:

- dogs with gastro-intestinal ulcers, renal disease, hepatic disorders, hypoproteinemia, dehydration, or cardiac disease;
- a known hypersensitivity to deracoxib;
- concurrent use of other NSAIDs or corticosteroids.

CAUTION:

No breed restrictions have been identified.

Not approved for use in cats.

For Veterinary Use Only.

Safety of this drug in dogs less than 4 months of age has not been established.

Animals being treated should be monitored for the occurrence of side effects as susceptibility varies with the individual. Adverse reactions for NSAIDs include gastrointestinal, renal and hepatic toxicity, hematological, neurological and dermatological abnormalities. If gastrointestinal or other side effects occur, treatment should be discontinued.

DERAMAXX should be used with caution in dogs with a known hypersensitivity to other NSAIDs.

Safety has not been established in breeding, pregnant or lactating dogs; therefore, deracoxib should not be used in these animals.

As with all NSAIDs, a complete veterinary exam including baseline hematology and serum biochemistry prior to the initiation of therapy and periodic reassessment during therapy are recommended.

While NSAIDs decrease prostaglandins that promote inflammation, they may also inhibit prostaglandins which maintain normal function. These anti-prostaglandin side-effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients. NSAIDs could therefore reveal the presence of disease that has been previously undiagnosed due to the absence of clinical signs. Patients with underlying renal disease for example may experience exacerbation or

decompensation of their renal disease while on NSAID therapy.

Appropriate monitoring procedures should be employed during all surgical procedures. The use of parenteral fluids during surgery for blood pressure support should be considered to decrease potential renal complications in dogs that have received NSAIDs preoperatively.

The concomitant use of other protein-bound drugs with DERAMAXX tablets has not been studied in dogs. Therefore, caution should be used when administering this drug with other protein bound drugs as they may compete for binding; dose adjustments may be necessary. As patients on concurrent diuretic therapy are at increased risk for NSAID toxicity, the use of Deramaxx in these patients is advised against.

WARNING:

KEEP OUT OF REACH OF CHILDREN. If accidentally swallowed, contact a physician.

ADVERSE REACTIONS:

Postoperative Pain and Inflammation Field Study

Two hundred and seven (207) dogs admitted to veterinary hospitals for repair of cranial cruciate injury were randomly administered DERAMAXX tablets or placebo. Drug administration began the evening before surgery and continued once daily for 6 days postoperatively. Dogs of forty-three (43) different breeds, 1-15 years old, weighing 3.2-64.1 kg 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 Field Study

Clinical Observation	DERAMAXX N=105	Placebo N=102
Vomiting	11	7
Diarrhea and soft stool	6	7
Hematochezia	4	0
Hematuria	2	0
Moist dermatitis	1	0
Otitis externa	2	0
Anorexia	0	1
Death	0	1

There was no evidence of problems with hemostasis or coagulation disorders in treated dogs. The results of this field study demonstrate that DERAMAXX tablets are well tolerated when administered at 3-4 mg/kg daily for 7 days to control postoperative orthopedic pain.

Osteoarthritis Pain and Inflammation Field Study

Two hundred and nine (209) client-owned dogs with clinical and radiographic signs of osteoarthritis were enrolled in this placebo-controlled, masked study. Tablets were administered by the owner at approximately 1-2 mg/kg/day for forty-three (43) consecutive days. 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 7.7-80.5 kg 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 Study

Clinical Observation	DERAMAXX N=105	Placebo N=104
Vomiting	4	4
Diarrhea and soft stool	4	3
Anorexia	2	3
Weight loss	1	2
Seizure	2*	2
Depression	1	0
Collapse/stupor	1	0
Lethargy	1	4
Pyoderma/dermatitis	2	2
Limping	0	1
Increased Alk Phos and ALT	1	0
Increased AST and GGT	0	1
Splenomegaly	1**	0

* One of these dogs withdrew from the study on Day 28 following brief seizure-like activity. Follow-up laboratory analysis revealed a neutrophilic leukocytosis, slightly decreased RBC count, panyhypoproteinemia with associated hypocalcemia and hypocholesterolemia. The dog recovered completely.

** This dog exhibited anorexia and lethargy on enrollment, with elevated WBC, amylase and AST. The dog was withdrawn from the study on Day 17 with anorexia, weakness, suspected diarrhea and splenomegaly, and died 1 month after exiting the study. Follow-up laboratory analyses revealed hypoalbuminemia, hypocalcemia, hyperphosphatemia, elevated AST, neutrophilic leukocytosis and non-regenerative anemia. Follow-up treatment included other anti-inflammatories and antibiotics.

Buccal mucosal bleeding time was normal in both treated and placebo groups. The results of this field study demonstrate that DERAMAXX tablets are well tolerated when administered at 1-2 mg/kg/day for the control of pain and inflammation associated with osteoarthritis.

SAFETY STUDIES:

Four safety studies were conducted with deracoxib in gelatin capsules; this formulation is 20% less bioavailable than the tablet formulation. In one tolerability study, dosages of up to 10-100 mg/kg, up to 25X the *ad usum* rate, were not fatal to dogs. Dogs received 10, 25, 50 or 100 mg/kg/d of micronized deracoxib in gelatin capsules, for 14, 11, 11 or 9 days, respectively. These exposures did not result in hepatobiliary or renal toxicity. Clinical signs of intestinal injury, melena and vomiting, resulted after exposures of 25-100 mg/kg (6.25-25X). Macroscopic and microscopic findings in the 10 mg/kg/d group included moderate diffuse congestion of gut-associated lymphoid tissue (GALT) and microscopic small intestinal ulcers in one dog, and small intestinal erosions in one other. One dog each in the 25 and 50 mg/kg/d groups exhibited macroscopic small intestinal erosions/ulcers; the 50 mg/kg/day dog also had gastric ulcers. At 100 mg/kg/d, all dogs exhibited gastric ulcers and small intestinal erosions/ulcers.

The severity of gastrointestinal injuries increased with dose and was due to non-specific, COX-1 inhibition.

In three separate laboratory studies, micronized deracoxib in gelatin capsules was demonstrated to be safe at therapeutic dosages when administered daily to dogs for 1, 3, or 6 months. In the 1 and 3 month studies, dogs received 0, 2, 4, or 8 mg/kg/day; no treatment-related effects were reported in any of the exposure groups. One male dog in the 3 month study, receiving 8 mg/kg, died of bacterial septicemia secondary to a renal abscess. In the 6 month study, dogs received 0, 2, 4, 8 or 10 mg/kg/day. There was an increased incidence of interdigital cysts in treated animals compared to controls. Mild elevations in mean BUN values were seen in the 8 and 10 mg/kg groups; no changes in creatinine were observed. Mild renal changes characterized by tubular degeneration/regeneration, atrophy and dilation were seen in two of four males receiving 10 mg/kg. No hepatobiliary, renal, gastrointestinal or coagulation abnormalities were reported at the evaluated COX-2 selective dosages of 2-8 mg/kg.

In a 6-month study, dogs were dosed with DERAMAXX tablets 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, physical examinations, ophthalmoscopic evaluations, macroscopic pathological examinations, hematology, or buccal mucosal 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. Treated male dogs did not gain weight at the same rate as controls; these differences were only significant in the 10 mg/kg group. After 6 months of treatment, elevations in mean blood urea nitrogen (BUN) values for dogs treated with 8 or 10 mg/kg/day were seen. No effects were found 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 gastro-intestinal, hepatic, or hematopoietic pathology at any of the doses tested.

During the clinical field trials, dogs receiving deracoxib were safely treated with a variety of medications.

Postoperative pain and inflammation field study: antibiotics, antiparasitics, sedative/anesthetic agents, opioids, anticholinergics, levofloxacin, and local bupivacaine

Osteoarthritis pain and inflammation field study: antibiotics, antiparasitics, sedative/anesthetic agents, opioids, anticholinergics, levofloxacin, topical antihistamines, and phenylpropranolamine

PALATABILITY STUDY:

DERAMAXX Flavor Tabs 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.

INFORMATION FOR PET OWNERS:

DERAMAXX (deracoxib) is a non-steroidal anti-inflammatory drug (NSAID) of the coxib class. It is indicated for the control of postoperative pain and inflammation, and for the control of pain and inflammation associated with osteoarthritis in dogs. As with any drug, side effects may occur in dogs being treated with DERAMAXX Flavor Tabs. Side effects are normally mild, but rare serious side effects can occur in dogs taking non-steroidal anti-inflammatory drugs (NSAIDs), including DERAMAXX. Side effects typically seen with NSAIDs include loss of appetite, vomiting, diarrhea, dark stools, depression and changes in drinking and urination. It is important to stop the medication and contact your veterinarian if you think your dog may have developed a side effect, or other medical condition while on DERAMAXX. Dogs undergoing prolonged treatment with any NSAID should be monitored periodically. For more information, consult your veterinarian.

PRESENTATION:

DERAMAXX Flavor Tabs are available in 25 and 100 mg tablet strengths in colour-coded packaging for oral administration to dogs.

25 mg round, biconvex, brownish half-scored tablets in an HDPE bottle containing 90 tablets

100 mg round, biconvex, brownish half-scored tablets in an HDPE bottle containing 90 tablets

STORAGE CONDITIONS:

DERAMAXX Flavor Tabs should be stored at 15-30°C, in a dry place.

 **NOVARTIS**

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