

FIROX[®] (firocoxib) CHEWABLE TABLETS

Affordable Pain and Inflammation Management for Dogs

Firox[®] (firocoxib) Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis (OA) and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs.

Firox[®]
(firocoxib) Chewable
Tablets



Proven Pain Relief

In a study of 1,000 dogs diagnosed with OA, 93% of dog owners rated their dog as “improved” and 86% of dog owners rated their dog as “happier” or “more active” after treatment with firocoxib.¹

How Firox Works

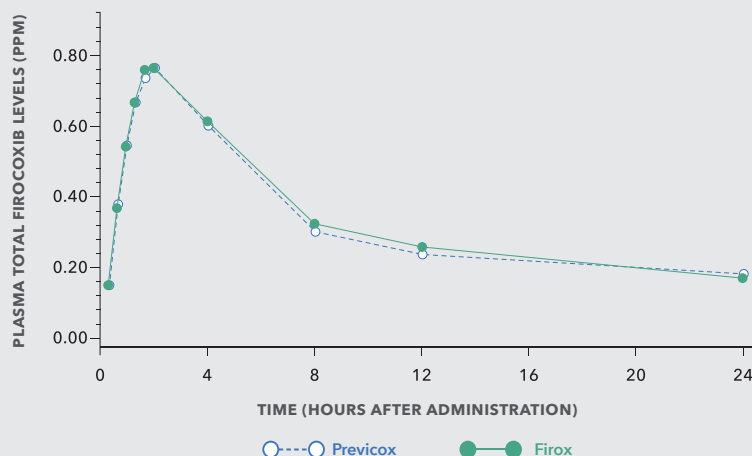
The active ingredient in Firox, firocoxib, is a cyclooxygenase-2 (COX-2) selective NSAID for use in dogs.¹ COX-2 is an enzyme responsible for the synthesis of inflammatory mediators and production of prostaglandin E2 (PGE2), which is necessary for sustaining the hyperalgesic response at sites of tissue inflammation.²

Bioequivalent to Previcox[®] (firocoxib) Chewable Tablets

Firox[®] (firocoxib) Chewable Tablets are bioequivalent to Previcox[®] (firocoxib) Chewable Tablets and deliver equivalent absorption and depletion for effective pain relief.

Firocoxib reaches peak plasma within 1 hour after administration (fasted)³

Plasma concentrations are maintained for 24 hours for once-daily dosing⁴



Mean plasma levels of firocoxib (µg/mL) in dogs after single oral administration of Firox vs. Previcox.⁴

Savings for Clients and Clinics

Reduces inventory costs

Encourages compliance with lower costs

Less expensive than Previcox[®] Chewable Tablets, offering significant savings and improved clinic profit potential

Helps to relieve financial burdens of clients that are treating chronic osteoarthritis (OA) in their dogs for the life of their pet

Affordable & Effective

Scored for easy splitting and accurate dosing of 5 mg/kg (2.27 mg/lb) body weight, once daily

Can be given with or without food

Chewable tablet with pork-liver flavoring

Available in 57 mg and 227 mg strengths in 60 count and economical 180 count bottles

IMPORTANT SAFETY INFORMATION: FIROX (firocoxib) Chewable Tablets are for use in dogs only. As a class, cyclooxygenase inhibitory NSAIDs like FIROX may be associated with gastrointestinal, kidney, or liver side effects. Dogs should be evaluated for pre-existing conditions and currently prescribed medications prior to treatment with FIROX, then monitored regularly while on therapy. Concurrent use with another NSAID, corticosteroid, or nephrotoxic medication should be avoided or monitored closely. For more information, please see full prescribing information.

⁴In-vitro studies have shown firocoxib to be highly selective for the COX-2 enzyme at 5 mg/kg/day; however it has not been established if increased specificity for COX-2 produces superior efficacy or safety.

¹Ryan WG, Moldave K, Carithers D. Clinical effectiveness and safety of a new NSAID, firocoxib: a 1,000 dog study. Vet Ther. 2006;7(2):119–126.

²Papich MG. Saunders Handbook of Veterinary Drugs: Small and Large Animals. 4th edition. St. Louis (Missouri): Elsevier; 2016.

³McCann M., Andersen D., Zhang D., et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in dogs with experimentally induced synovitis. AJVR 2004; Vol 65, No. 4: 503-512.

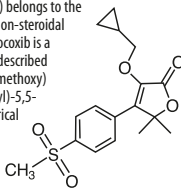
⁴Data on File.

Firox™ (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: Firox (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 $C_{21}H_{24}O_5S$, and the molecular weight is 336.4. The structural formula is shown at right:



Pharmacokinetics: The absolute bioavailability of Firox (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 ($CL_{systemic} = -0.4$ L/hr/kg). Despite a high level of plasma protein binding (96%), firocoxib exhibits a large volume of distribution (V_d), of total drug $= \sim 4.6$ 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 Firox with food delays drug absorption (T_{max} from 1 to 5 hours) and decreases peak concentrations (C_{max} from 1.3 to 0.9 mcg/mL). However, food does not affect the overall oral bioavailability at the recommended dose.

Indications: Firox (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 and orthopedic surgery in dogs.

Dosage and Administration: Always provide the Client Information Sheet with prescription. Carefully consider the potential benefits and risks of Firox and other treatment options before deciding to use Firox. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage of Firox (firocoxib) for oral administration in dogs is 2.27 mg/lb (5.0 mg/kg) body weight once daily as needed for osteoarthritis and for 3 days as needed for postoperative pain and inflammation associated with soft-tissue and orthopedic surgery. The dogs can be treated with Firox approximately two hours prior to surgery. The tablets are scored and dosage should be calculated in half tablet increments. Firox Chewable Tablets can be administered with or without food.

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

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 Firox Chewable Tablets.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

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 ulceration and/or gastrointestinal perforation, concomitant use of Firox Chewable Tablets with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein bound drugs with Firox 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 Firox 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 Firox, 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 Firox 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 firocoxib 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	Firocoxib Chewable Tablets n=128	Active Group* 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

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 firocoxib 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 Studies

Adverse Reactions	Firocoxib Group n=127	Control Group* n=131
Vomiting	5	6
Diarrhea	1	1
Bruising at Surgery Site	1	1
Respiratory Arrest	1	0
SC Crepitus in Rear Leg and Flank	1	0
Swollen Paw	1	0

*Sham-dosed (pilled)

Orthopedic Surgery: In a controlled field study evaluating orthopedic postoperative pain and inflammation, 226 dogs of various breeds, ranging in age from 1 to 11.9 years in the firocoxib-treated groups and 0.7 to 17 years in the control group were evaluated for safety. Of the 226 dogs, 118 were given firocoxib 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 a total of three 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 Orthopedic Surgery Postoperative Pain Field Study

Adverse Reactions	Firocoxib Group n=118	Control Group* n=108
Vomiting	1	0
Diarrhea	2**	1
Bruising at Surgery Site	2	3
Inappetence/Decreased Appetite	1	2
Pyrexia	0	1
Incision Swelling, Redness	9	5
Draining Incision	2	0

A case may be represented in more than one category. *Sham-dosed (pilled). **One dog had hemorrhagic gastroenteritis.

Post-Approval Experience (Rev. 2009): The following adverse reactions are based on post-approval adverse drug event reporting. The categories are listed in decreasing order of frequency by body system:

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal perforation, hematemesis, hematochezia, weight loss, gastrointestinal ulceration, peritonitis, abdominal pain, hypersalivation, nausea

Urinary: elevated BUN, elevated creatinine, polydipsia, polyuria, hematuria, urinary incontinence, proteinuria, kidney failure, azotemia, urinary tract infection

Neurological/Behavioral/Special Sense: depression/lethargy, ataxia, seizures, nervousness, confusion, weakness, hyperactivity, tremor, paresis, head tilt, nystagmus, mydriasis, aggression, uveitis.

Hepatic: elevated ALP, elevated ALT, elevated bilirubin, decreased albumin, elevated AST, icterus, decreased or increased total protein and globulin, pancreatitis, ascites, liver failure, decreased BUN

Hematological: anemia, neutrophilia, thrombocytopenia, neutropenia

Cardiovascular/Respiratory: tachypnea, dyspnea, tachycardia

Dermatologic/Immunologic: pruritis, fever, alopecia, moist dermatitis, autoimmune hemolytic anemia, facial/muzzle edema, urticaria

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

To report suspected adverse drug events, for technical

assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Information For Dog Owners: Firox, 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 Firox 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: Firox (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 firocoxib chewable tablets 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 firocoxib chewable tablets compared with the active control. At the study's end, 87% of the owners rated firocoxib chewable tablets-treated dogs as improved. Eighty-eight percent of dogs treated with firocoxib chewable tablets were also judged improved by the veterinarians. Dogs treated with firocoxib chewable tablets 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 firocoxib chewable tablets-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 firocoxib chewable tablets 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 firocoxib chewable tablets-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.

A multi-center field study with 226 client-owned dogs of various breeds, and ranging in age from 1 to 11.9 years in the firocoxib chewable tablets-treated groups and 0.7 to 17 years in the control group was conducted. Dogs were randomly assigned to either the firocoxib chewable tablets or the control (sham-dosed-pilled) group for the control of postoperative pain and inflammation associated with orthopedic surgery. Surgery to repair a ruptured cruciate ligament including the following stabilization procedures: tibial suture and/or imbrication, fibular head transposition, tibial plateau leveling osteotomy (TPLO), and/or the top technique. The study ($n = 220$ for effectiveness) demonstrated that firocoxib chewable tablets-treated dogs had significantly lower need for rescue medication than the control (sham-dosed-pilled) in controlling postoperative pain and inflammation associated with orthopedic surgery.

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 polyarthritis 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 (1 X) dose of 5 mg/kg, on histopathologic examination, three out of six dogs had minimal peritoneal 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 peritoneal 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 peritoneal 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 peritoneal 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 below 86°F (30°C). Brief excursions up to 104°F (40°C) are permitted. Use half tablet within 90 days. Contact an SDS, call 1-866-591-5777.

How Supplied: Firox 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 60 count and 180 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 Cyclo-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E2 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 in NADA 141-230.

Manufactured for:

Norbrook Laboratories Limited, Newry, BT35 6PU, Co. Down, Northern Ireland. www.norbrook.com
1-866-591-5777

Approved by FDA under ANADA # 200-722

Firox™ is a trademark of Norbrook Laboratories Limited

